THE Journal Kansas Medical Society

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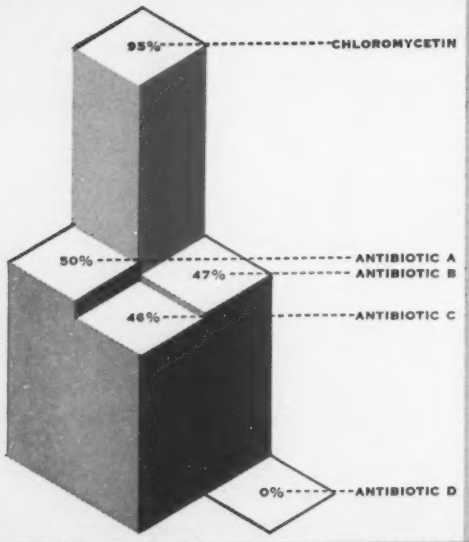
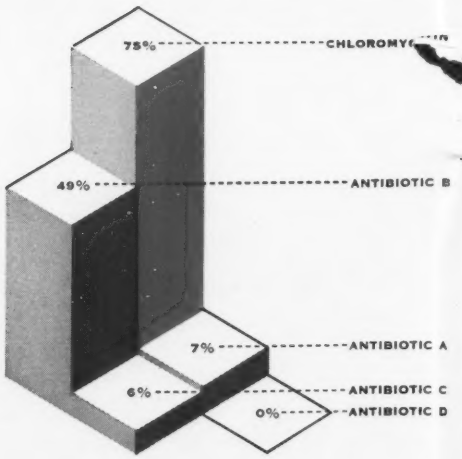
1956

VOL LVII
NO IX

SENSITIVITY OF COMMON PATHOGENS TO CHLOROMYCETIN AND FOUR OTHER MAJOR ANTIBIOTIC AGENTS*

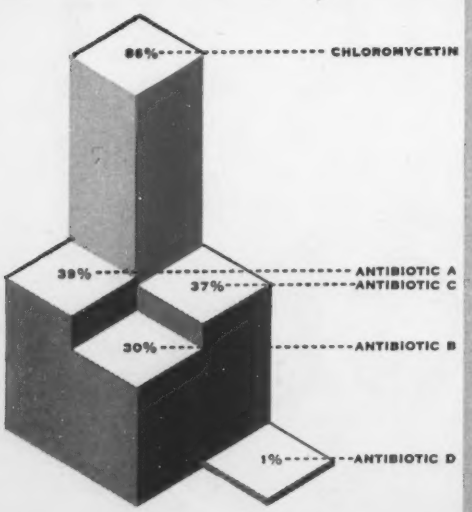


ESCHERICHIA COLI
(148-227 STRAINS)

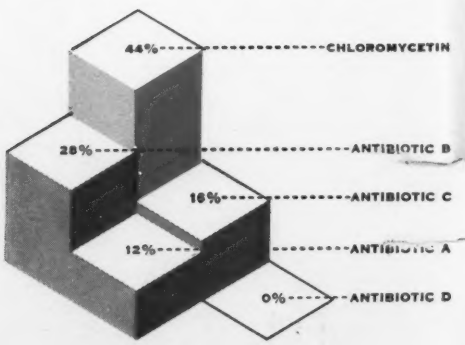


BACILLUS PROTEUS
(63-104 STRAINS)

AEROBACTER AEROGENES
(143-248 STRAINS)



PSEUDOMONAS AERUGINOSA
(69-70 STRAINS)



*This graph, based on *in vitro* studies, is adapted from Horton and Knight.[9]

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Therapeutic advantages of CHLOROMYCETIN (chloramphenicol, Parke-Davis) are especially appreciated when mixed infections are encountered because it provides highly effective antibiotic action both against gram-negative and against gram-positive pathogens.[1-7] CHLOROMYCETIN also acts against many pathogens which may grow when originally sensitive organisms have been suppressed.[2]

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CHLOROMYCETIN is a potent therapeutic agent, and because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References: (1) Felix, N. S.: *Pediat. Clin. North America* 3:317, 1956. (2) Joron, G. E.; Fowler, A. F.; de Vries, J.; Reid, G., & Mathews, W. H.: *Canad. M. A. J.* 73:956, 1955. (3) Weil, A. J., & Stempel, B.: *Antibiotic Med.* 1:319, 1955. (4) Perry, R. E., Jr.: *North Carolina M. J.* 16:567, 1955. (5) Jones, C. P.; Carter, B.; Thomas, W. L., & Creadick, R. N.: *Obst. & Gynec.* 5:365, 1955. (6) Murphy, F. D., & Waisbren, B. A., in Murphy, F. D.: Medical Emergencies: Diagnosis and Treatment, ed. 5, Philadelphia, F. A. Davis Company, 1955, p. 557. (7) Altemeier, W. A.; Culbertson, W. R.; Sherman, R.; Cole, W.; Elstun, W., & Fultz, C. T.: *J.A.M.A.* 157:305, 1955. (8) Horton, B. F., & Knight, V.: *J. Tennessee M. A.* 48:367, 1955.

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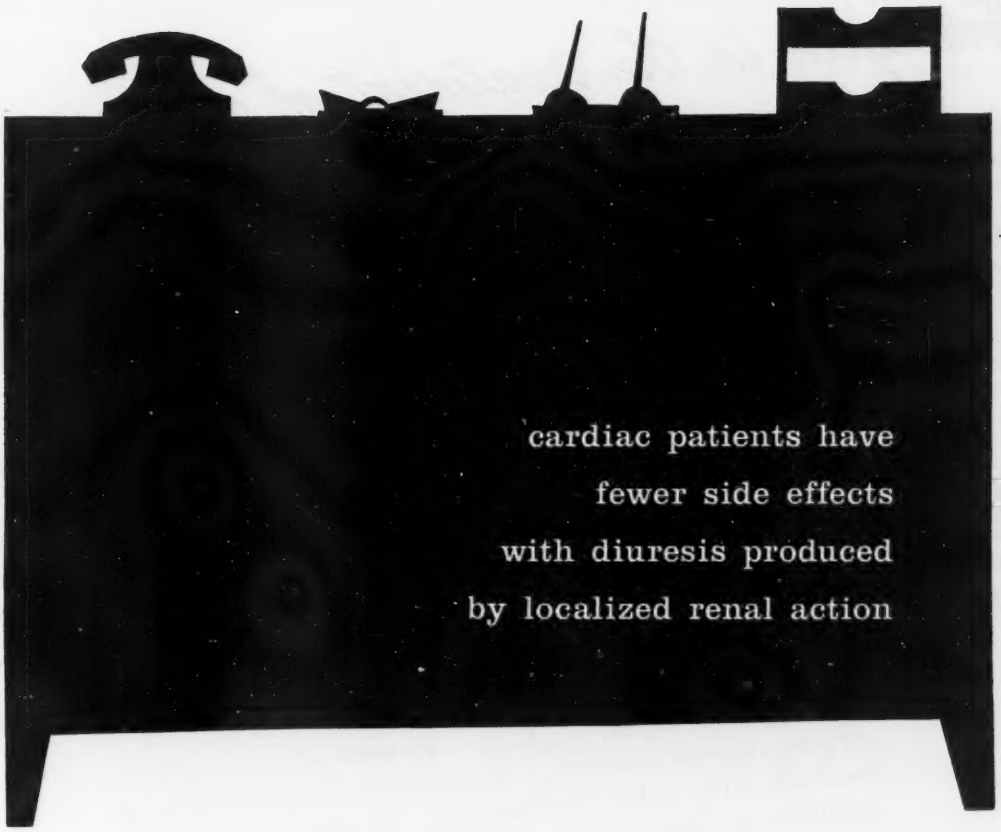

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*Erythromycin in the treatment of osteomyelitis**

8/3/55

CASE SUMMARY

On 6/2/55, patient, male, age 28, fell on an old fracture and refractured the middle third of the right femur, superimposed on an old osteomyelitis.

On 7/7/55, the wound was saucerized and a hemolytic S. aureus (coag. +) was isolated from the osteomyelitis. Disc sensitivities were: penicillin, 10 units; erythromycin, 10 mcg.; tetracycline, 10 mcg.

On 7/15, the patient was placed on erythromycin therapy 400 mgm. q. 6. h. Patient afebrile after erythromycin started. X-rays showed evidence of healing with callus formation. No septicemia and clinical evidence indicates control of the infection.

On 8/3, the cast was removed and leg recast. Wound was in good condition with minimal drainage.

Diagnosis: fracture middle third of right femur, complicated by osteomyelitis.

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* *Communication to Abbott Laboratories*

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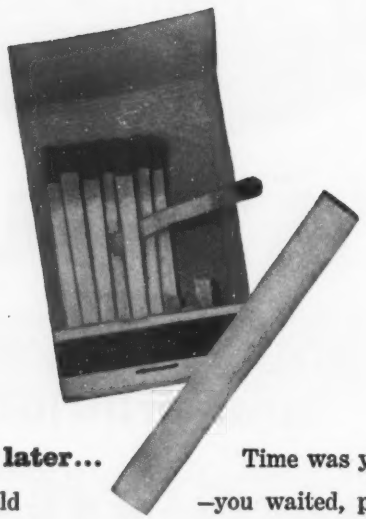

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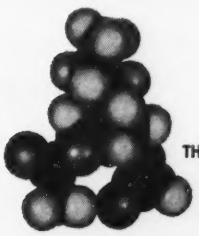

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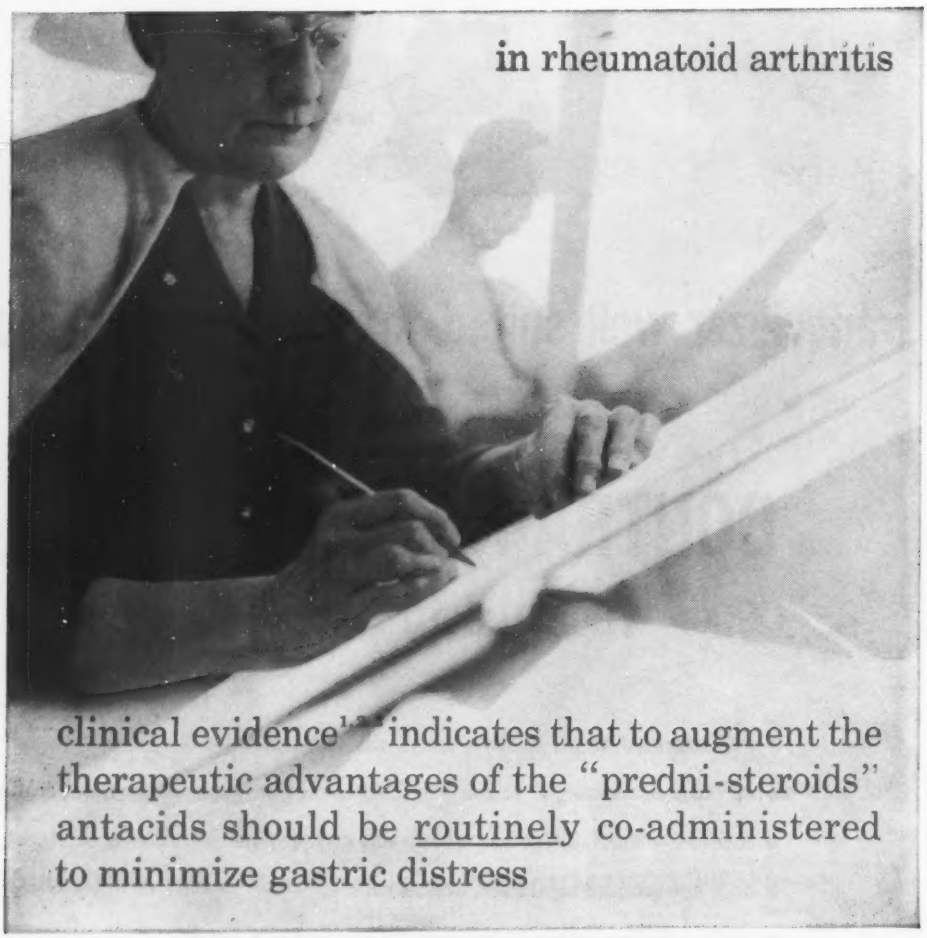
in rheumatoid arthritis
clinical evidence[1,2,3] indicates that to augment the therapeutic advantages of the "predni-steroids" antacids should be routinely co-administered to minimize gastric distress

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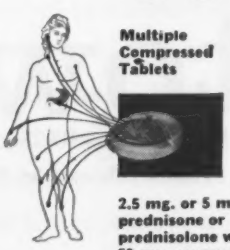

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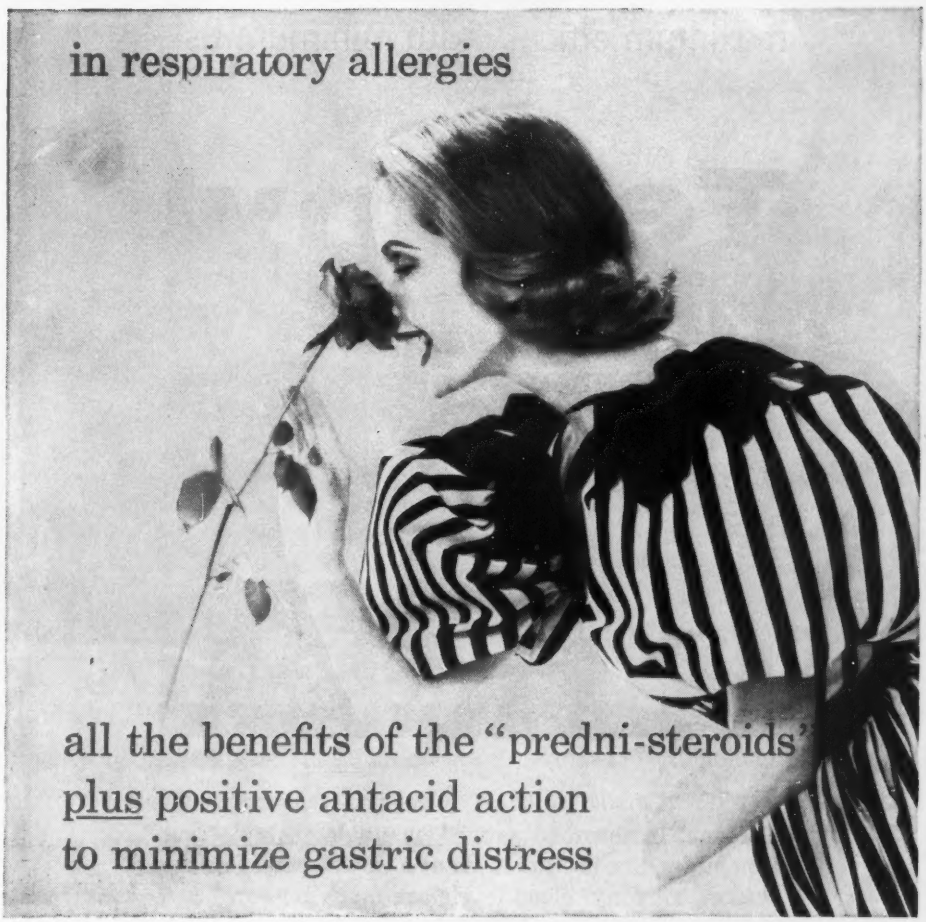
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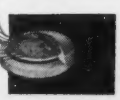

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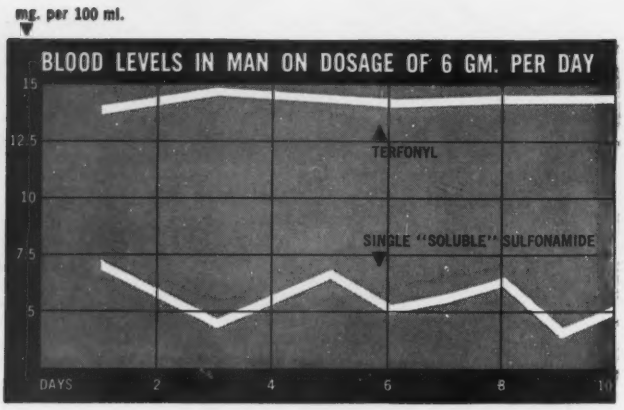

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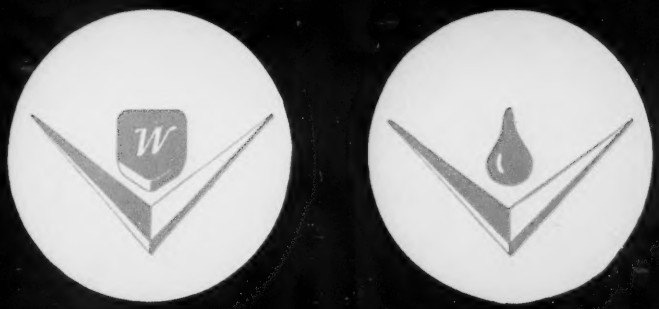

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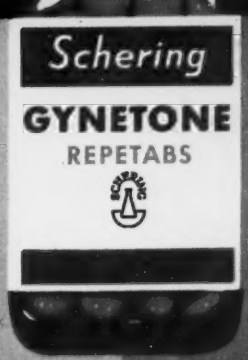

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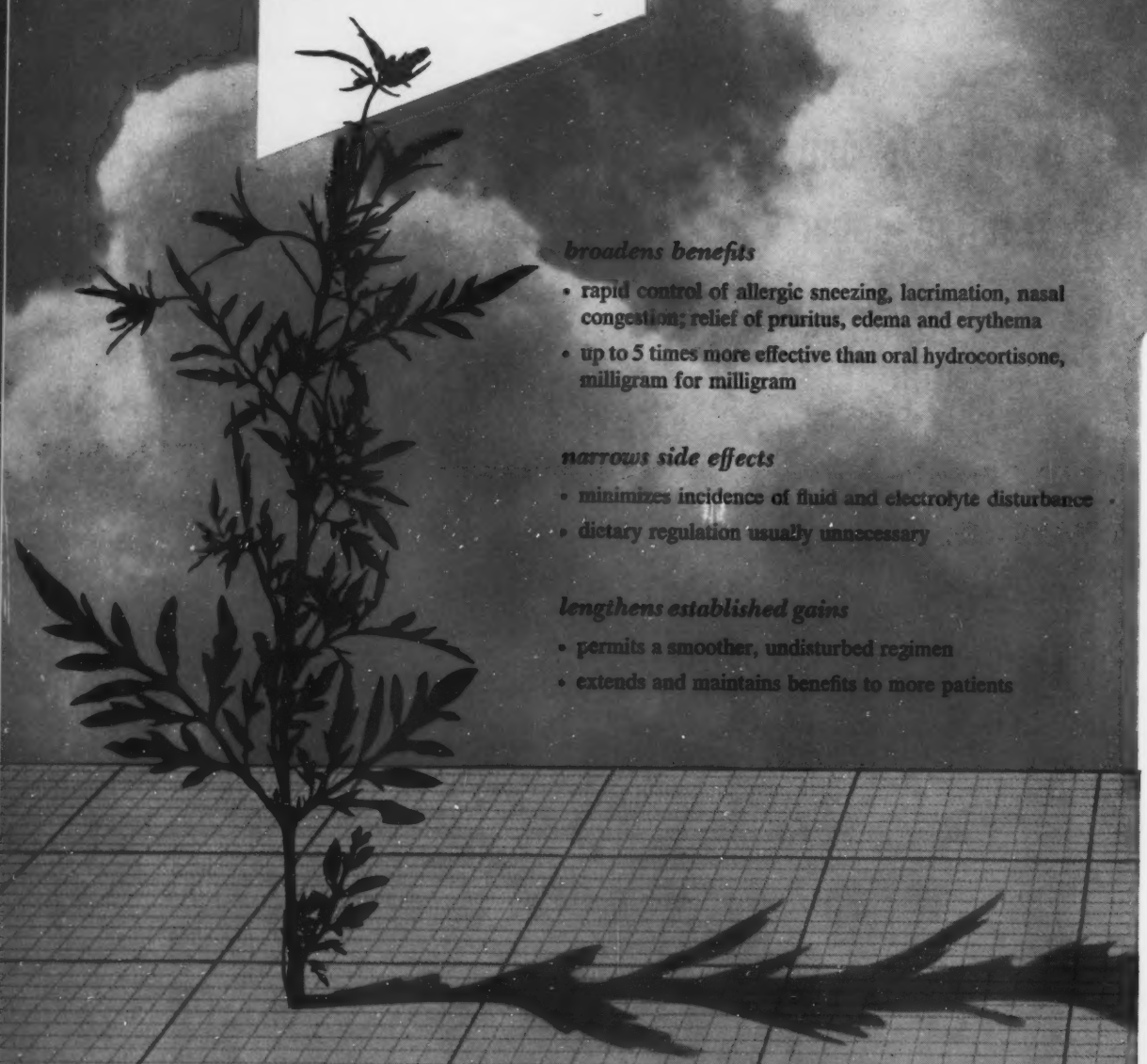

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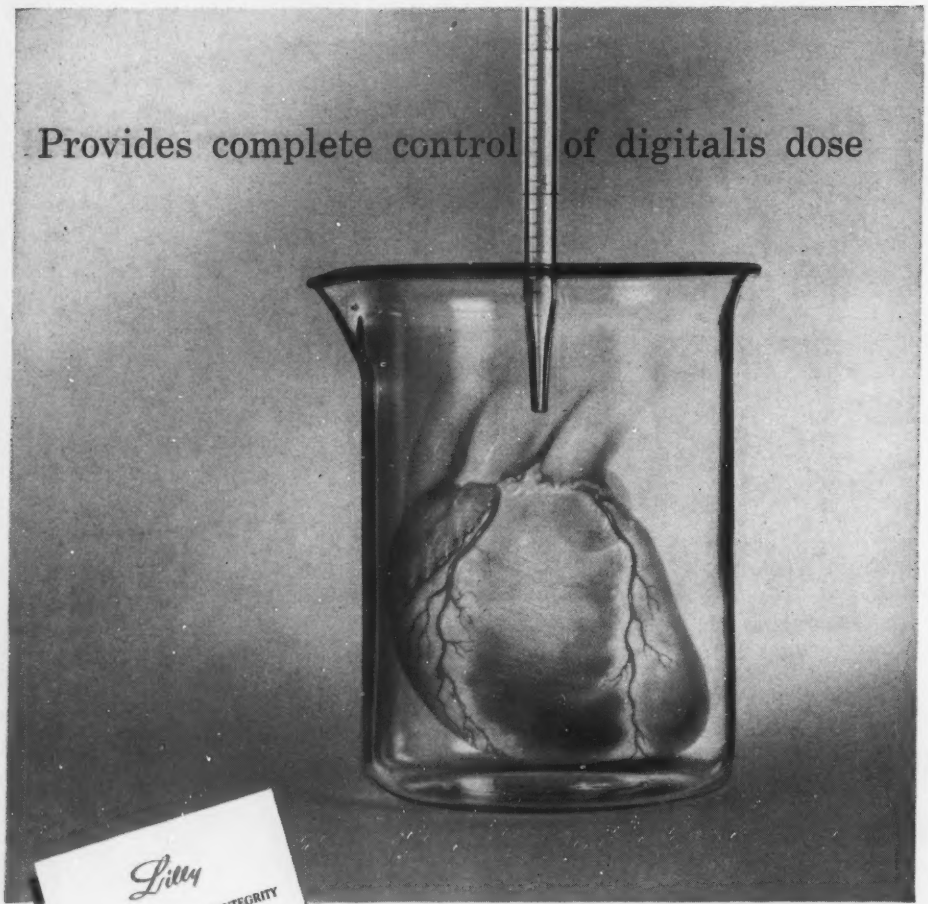

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Rehabilitation

Restoration of Function after Fractures Is an Important and Sometimes Neglected Feature of Their Treatment

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Rehabilitation of fractures of the spine presents problems of a character and divergence not presented by fractures of long bones. Long bones, mechanically, have as their only function the ability to transfer weight. The spine also must transfer weight but must function in addition as a highly mobile column, and as a further duty must protect the spinal cord. To provide the means of performing these additional functions, the architecture of the spine must be unique and is expressed by the intricate form of the vertebrae, by their multiple areas of contact, by their relationship to the intervertebral discs, and by the intervertebral discs whose structural characteristics are dissimilar to any other tissue in the body.

Injuries to the articular surfaces of the vertebrae may cause pain in a manner similar to that produced by comparable injuries to the joints of the long bones. However, because vertebrae present so many areas of contact, these opportunities are multiplied. Also, the alteration of the shape of any part of a vertebra, such as a compression of its body, will result in a derangement of the mechanics of several joints instead of only one or two in long bones. The intervertebral disc, because of the structural mobility required by its function, is highly vulnerable to trauma; and the spinal cord and nerve roots encased within the vertebrae for protection may, because of the very contiguity of the protection, suffer severe and irreparable damage. These factors set aside spine injuries as a specific problem.

Residual fractures of the thoracic area rarely require treatment. Mobility in this area is limited. The spine is supported and stabilized somewhat by the ribs, and there is little weight to be carried. Occasionally a brace is advisable but rarely required. In the lumbar area, however, with a great range of motion between the vertebra and with the torso load to be carried, occasionally a fusion may be required if a brace gives inadequate relief of disability. In all areas of the spine, if an intervertebral disc has been sufficiently damaged, there may be a definite residual disability. The occasional course of healing results in a bony bridging of the disc ankylosing the adjacent vertebra with relief of symptoms. If this happy intervention of healing is denied, then support either by a brace or by surgical fusion of the adjacent vertebra may be indicated. This procedure may be advised with confidence in a good end result. Loss of motion between two or three vertebrae, even in the cervical or lumbar area, results in little disability, and the relief from pain is adequate compensation for whatever loss of motion eventuates.

Residual fractures of the cervical spine, providing the posterior elements are competent and not dis-

This is the third article in a four-part series. Part I was published in the July issue of the Journal, Part II appeared in August, and the final installment will be printed in October.

placed, rarely require treatment. However, if without paraplegia there is an ununited fracture through the pedicles, or if there is an anterior dislocation of a vertebra, a severe instability exists and a paraplegia is impending, to be precipitated by minor trauma. In such a situation the patient's luck may be considered to be exhausted and a spinal fusion advised.

Not infrequently the sequelae of the treatment of spine fractures are more disabling than if the fracture had been left untreated. I am certain you have heard many old physicians say that their fracture results were much better before x-rays were available than they were after x-rays were easily obtained. If there is any group of fracture cases where this dictum is pertinent, it is in compression fractures of the bodies of the lower thoracic and lumbar vertebrae.

For years we have been placing these patients in hyperextension casts with postreduction x-ray evidence of excellent correction of the compression. Many have been ambulatory early, exercising and even working with minimal complaint while immobilized. However, after the cast has been removed and the subsequent brace discarded, symptoms continue and multiply. Usually the subjective complaint has been localized in the lumbosacral area rather than in the area of fracture, and it has been this localization we have ignored.

The cause of the lumbosacral pain is easily explained; it is secondary to the hypertension cast and is not secondary to the fracture per se. The lumbar lordosis inherent in the upright posture is the parent of most of the low back complaints in the so-called normal back. In a hyperextension cast this lordosis is increased, and it is maintained for months in this augmented position. The ligaments and the intervertebral discs involved eventually succumb to the constant tension and pressure, and a permanent disability of the lumbosacral area is the sequela of the treatment of a fracture of a lumbar or thoracic vertebra.

Since we have had the courage to accept a moderate compression of a vertebral body and have ceased attempting to correct it, we have had much improved results. Our present treatment of a moderate compression of a vertebral body is a few days' bed rest followed by a light brace, occasionally only a corset, early ambulation, and function. We make an earnest attempt to ignore the fracture, and we have aided our patients best by treating them least.

Fractures of the spine with paraplegia, often quadriplegia, present a distressing, discouraging problem. The most that can be offered to these unfortunate patients is the effort to rehabilitate them around their disability, not relieving them of it. It is occasionally amazing what can be accomplished by the exercise of a will to do, patience, opportunism, and training. Certainly if the upper extremities are paralyzed, little can be done except in the occasional case where a muscle transplant, a wrist fusion, or a bone block in a thumb may increase the functional value of a hand.

If, however, adequate function remains in the upper extremities, and if the patient has a determination to rehabilitate himself, much can be done to assist him. The severe clonic contractures frequently exhibited by these patients can be controlled by rhizotomy or better by alcohol injections intrathecally. Fixed contractures can be released by division or lengthening of tendons. Crutches and braces may allow ambulation. Training frequently results in an automatic bowel and bladder. Invention, substitution, and opportunism frequently solve the problems of a paraplegic's job, and many become adequate employees. The aptitude tests and vocational training afforded by the Division of Vocational Rehabilitation have proved beneficial in training these patients, and this help has been readily available.

LIMITATION OF MOTION OF JOINTS

It is almost axiomatic that any fracture will result at least temporarily in some limitation of range of motion in contiguous joints. This complication is more frequently found by the patient than considered by the physician when treatment is instituted. There has been a valuable evolution in the treatment of fractures which has tended to lessen this serious complication, inspired by this fear of the patient and also by the aspiration of the thoughtful physician. However, even with improvement resulting from progressive treatment techniques, the frequency and degree of limitation of motion is too often a major calamity. Treatment procedures based on early and frequent joint movements are not yet practiced sufficiently to place this complication in the limbo it deserves.

Fracture may cause limitation of motion in a contiguous joint as a result of:

1. Adhesions within the joint capsule.
2. Adhesion between the synovia-capsule structures and the articular surfaces.
3. Contractures of muscles immobilized in an unphysiological position.
4. Incarceration of muscle in the healing process at the fracture site.

This group of fracture complications may be treated better by prevention than by correction. However, some form of stretching is indicated if there is a significant resulting limitation of motion which is secondary to adhesions in the synovia-capsule mechanism or muscle contracture. If stretching is to be instituted, a clear distinction must be made between synovia-capsular adhesion and the pathology in those cases in which muscle or tendon has become incorporated

in a callous scar. Adhesions as a result of inactivity and disuse of the synovia-capsular tissues are fine and friable and may be easily broken up by stretching. On the other hand, adhesions resulting from organized hemorrhage will be heavy fibrous tissue of great strength. An attempt to stretch a firm scar of this type might easily result in multiplying the complication.

Organized scar will maintain its integrity in the face of vigorous assault. Devitalized normal tissue may give way as is attested by many patellae resulting from forceful flexion of knees whose quadriceps were bound in the scar of a fractured femur. Therefore, before any stretching maneuvers are employed to increase the range of motion in a joint, the character and location of the pathology must be carefully evaluated. Stretching offers no solution for those cases in which the pathology is organized scar incorporating the motors of a joint.

Quite certainly the most valuable assist in regaining lost joint range is a purposeful function which produces stretching. If the part to be treated can be employed in some remunerative, necessary, or pleasurable task it will be exposed to more consistent and effective stretching than can be supplied in any other manner. It has been noted that removing the factor of necessity, as accomplished by industrial compensation payments, frequently results in retarded recovery. Thoughtful ingenuity on the part of the physician and his patient will frequently develop an activity which will be therapeutically beneficial. Piano playing, typewriting, dishwashing, card playing, sewing, working with hand tools, etc., employed several hours a day, will do more to improve a stiff hand than the most efficient physical therapist can accomplish in a daily half-hour treatment. Similar purposeful uses for the other joints of the extremities and spine can be developed by a little consideration of the problem in the light of the patient's capacities, training, and inclinations.

In re-establishing lost joint motion, the value of an experienced physical therapist should not be under-rated, particularly in the treatment of early cases. The patient frequently requires the patience, guidance, and confidence-inspiring services of a physical therapist. However, after painless movement in even a limited range has been achieved, active purposeful motion is superior therapy. The physical therapist then should treat the patient frequently enough to maintain his interest in his improvement and to devise new active functions to maintain constant attack on the adhesions.

Mechanical stretching devices maintaining constant attack on the capsule-synovial adhesions can be effective. Turnbuckle, spring, rubber, or traction appliances exert their force directly at the site of the contracture because the protection of the muscles motivating the joint is eliminated early by their tiring. Ingenuity is required by the physician in developing these mechanical aids as each must be developed for each individual case. When these constant forces are employed, it must be remembered that new adhesions may be formed in the contralateral tissues. New contralateral adhesions can be prevented by an occasional repetition of the full range of attainable motion in the joint.

Cases which have a limitation of joint motion secondary to a muscle or tendon being entrapped in the scar of the callous offer a poor prognosis for effective improvement. In the upper extremity, other than a poor cosmetic result, little disability eventuates, but a marked limitation of flexion in a knee can be disabling. Stretching procedures are ineffective, and surgical measures have been disappointing. Occasionally flexion can be recouped in a knee by resection from the patella of the three deep bellies of the quadriceps, leaving the long head to activate extension of the joint. In those patients requiring maneuverability instead of stability, it is a procedure offering a possibility of improvement. Probably, in most cases where the muscles are importantly enmeshed in scar, acceptance of the resultant disability with development of adroit maneuvers to circumvent its effect is the approach of choice.

Not infrequently, particularly in Pott's fractures and fractures of the humerus, limited joint motion is primarily a result of contracted muscles not adherent in the scar. The pathology in these cases results from long periods of immobilization with one group of muscles completely relaxed and the opponents taut. Because of the resiliency of muscle tissue, relaxed muscles rapidly contract while the taut ones extend and become fixed in these lengths to accommodate their maintained positions. For this reason it is important, particularly in Pott's fractures, that the joint be immobilized with the muscle antagonists in a neutral position. If contractures of the calf have occurred in an ankle fracture, exercises and passive stretching are helpful, but again active function is particularly valuable treatment. The heel may be raised by applying ⅛ to ¼ inch layers of leather or balsa wood until the foot can comfortably carry weight. Then as tolerable, following walking, a layer at a time may be removed from the heel until the normal heel height has again been gained.

CONCLUSION

May I again point out to you that there are many uncertainties and that there are many unavoidable, unhappy results in the treatment of fractures. On

the other hand, there are few poor results which cannot be ameliorated or rehabilitated by further definitive treatment. Each poor result will present itself as a specific entity, and your solution of that problem must be based on the answer to an equation. The factors in that equation are a knowledge of the available corrective measures, an evaluation of the extent of the existing disability, and a decision on whether correction is worth the expenditure of time, money, and pain. You still must meditate with Hamlet, "whether it is nobler to suffer the slings and arrows of outrageous fortune, or to take arms against a sea of troubles and by opposing end them."

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Heart Disease

A Study of Blood Ammonia Levels in Congestive Heart Failure with Report of Three Cases

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Disorientation, delirium, frank psychosis, tremors, and even more complicated pictures of mental and neurological abnormalities have long been noted during and as a terminal event of congestive heart failure. So frequently and for so long have these signs been noted that seldom is an explanation asked for. When the matter is questioned, the traditional interpretation of these central nervous system manifestations utilizes the obvious state of hypoxia to explain the phenomena. Doubtless the diminished oxygen supply to the various organs of the body must result in profound and complex metabolic changes contributing to nervous system changes. In spite of the reasonableness of this exposition, it has been questioned of recent date. The belief that other factors contribute certain features is now more convincing.

For several years we have been impressed by the striking similarity in mental and neurological abnormalities seen in the patient in hepatic coma and the patient suffering severe congestive heart failure. Emotional irritability, confusion, delirium, agitation, flapping tremor, lethargy, and weakness are common to both conditions. Clarification of the pathogenesis of these complicating signs in severe liver failure immediately suggests application of the same explanation in congestive heart failure. Liver dysfunction and abnormalities coexisting in heart failure have been the subject of interest for some time, so the relationship seems less remote.

Both anatomical and functional alterations of the liver in patients with congestive heart failure have been reviewed by many investigators. Anatomical changes include dilatation of the sinusoids and narrowing of the liver cords in the central area of the lobules, necrosis of the central cells, condensation of reticulum in the degenerated central areas, marked thickening of the walls of the central and hepatic veins, as well as fibrosis of the liver with active fibroblastic proliferation. The degree of hepatic necrosis varies with the degree and severity of congestive heart failure. So-called liver function tests are also deviated from the normal. Bromsulfalein excretion is usually impaired. Mild elevation of serum bilirubin is common, but clinical jaundice is rare in the absence of pulmonary infarction. The urine urobilinogen is often elevated. Serum albumin, alkaline phosphatase, thymol turbidity, and cephalin cholesterol flocculation values are usually normal, however.

Blood ammonia levels were determined in 26 patients, and the clinical courses of three are reported. Possible explanations are given for elevated blood ammonia levels, potential hazards of therapy are discussed, and the need for additional investigative studies is stressed.

Innumerable metabolic abnormalities surely exist during any given episode of severe liver failure. The

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complexities of these deviations still largely defy actual measurement. This is to be expected in a situation involving a structure with such broad functions as the liver. Its activity in protein metabolism has recently attracted much interest, chiefly because of the repeated observation that blood ammonia levels are usually quite elevated in liver failure and hepatic coma. Examination of the literature concerning this subject points up the curious fact that although the fundamental knowledge concerning the problem has been known to biochemists and physiologists for many years, clinical application has been attempted only recently.

It has been well established by experimental work that the liver is the principal site for the deamination of ammonia containing compounds absorbed by the intestine. Folin and Dennis[12] demonstrated that the ammonium content of the portal blood was significantly higher than that of the peripheral circulation. More than 30 years ago Matthews[13] reported that Eck fistula dogs fed a high protein diet developed the syndrome of "meat intoxication." It is now clear that this syndrome has a remarkable similarity to hepatic coma in humans. In fact, comparable demonstrations in humans with portocaval shunts have been made by McDermott and Adams,[14] and Havens and Child.[15] The supposition that high blood ammonia concentrations in the portal vein, resulting from the absorption of nitrogenous substances from the intestinal tract, by-pass the normal urea synthesizing mechanism in the liver is reasonable. It must be further theorized that these high levels of ammonia, now present in the systemic circulation, exert a deleterious effect upon the central nervous system producing the syndrome which we call hepatic coma.

Bessman and Bessman[16] have suggested that high levels of ammonia in the blood result in the increased formation of glutamine from alpha keto glutarate with a decreased amount of the latter compound available in the central nervous system to take part in the Krebs cycle. It should be reemphasized that an elevated blood ammonia level may well be only one of multiple metabolic and biochemical abnormalities occurring in hepatic failure and coma. Whether the mental and neurological changes in this syndrome can be charged directly and specifically to ammonia ion intoxication is to date still unsettled.

Sherlock and others,[17] finding elevated blood ammonia levels in patients with cirrhosis who evidenced good hepatic cellular function, convincingly suggested portal systemic shunting of ammonia rich blood by and around the normally functioning liver cell. The effect upon the central nervous system, they have termed portal systemic encephalopathy. Here the situation is one of circulatory failure, after a fashion, because of abnormal collateral shunting of portal blood either around or through the liver. In patients with acute severe hepatocellular damage, the explanation must be altered. Here the liver is so severely damaged and parenchymal cell function is at such a low ebb that the liver acts as a "sieve," failing to perform its function of deamination of nitrogenous materials and passing these on into the systemic circulation.

The above mentioned mechanisms may be operating in patients with congestive heart failure. Severe liver damage resulting from congestive heart failure may interfere with the deamination of ammonia containing compounds brought to the liver by the portal vein. Increased pressure in the hepatic veins and sinusoids, as a result of congestive failure, may increase portal vein pressure with a resultant increase in the flow of the ammonia rich portal blood through portocaval collateral vessels such as the gastroesophageal, hemorrhoidal, and superficial abdominal veins. Thus it is seen that in congestive heart failure there are two mechanisms which may result in increased systemic blood ammonia concentrations.

The possibility that patients with congestive heart failure are prone to develop "ammonia intoxication" assumes more than academic interest. Three of the main therapeutic agents used in the treatment of these patients—ammonium chloride, cation exchange resins, and Diamox—have been shown to be precipitating agents in the production of hepatic coma in patients with liver disease. The possibility that these therapeutic agents may actually be more harmful than beneficial in patients with severe passive congestion of the liver due to cardiac failure must be considered.

Elevated blood ammonia levels have already been reported in patients with congestive heart failure. In a series of nine patients Bessman and Evans[21] found elevated blood ammonia levels in eight. It is the purpose of this report to present our observations of blood ammonia levels in patients with congestive heart failure studied during the past 12 months.

MATERIAL AND METHODS

Fasting blood ammonia cencentrations were performed in 26 patients who were hospitalized because of congestive heart failure. There were 15 males and 11 females. Their average age was 56.6 years with a range from 32 to 73 years. Ten patients had arteriosclerotic heart disease, eight had rheumatic heart disease, six had hypertensive heart disease, two had cor pulmonale, two had syphilitic heart disease, and one had kyphoscoliotic heart disease. Three patients had two types of heart disease.

All of the patients in this study had hepatomegaly. The degree of liver enlargement was determined by palpation and percussion. The liver was considered

to be slightly enlarged if the inferior border was detectable up to four centimeters below the right costal margin in the midclavicular line. If the border was four to eight centimeters below the costal margin, the hepatomegaly was classed as moderate. Markedly enlarged livers were those whose lower borders extended over eight centimeters below the right costal margin. Two patients had slightly enlarged livers, 19 had moderately enlarged livers, and five had markedly enlarged livers. Eleven of the 26 patients showed some abnormality of standard liver function tests. None of the patients had dilated abdominal veins, hemorrhoids, esophageal varices, or other evidence of portocaval collateral circulation. Abnormally high venous pressures were recorded in 11 of 13 patients in whom they were performed.

The blood ammonia determination was carried out by a modification of Conway's method.[22] Venous blood was introduced into a saturated solution of potassium carbonate in the outer chamber of a Conway dish. The inner chamber containing 0.0002N hydrochloric acid with methyl red methylene blue indicator was titrated with 0.0005N barium hydroxide after diffusion was allowed to proceed at room temperature for 15 minutes. A blank and a standard solution of ammonium sulfate were run simultaneously with the unknown. The details of this determination are reported elsewhere.[23] In all cases, the diffusion process was started within five minutes after the blood was shed. It has been shown that the ammonia content of the blood is stable up to 20 minutes after the blood is shed.[23]

In our laboratory normal values for fasting blood ammonia range from 50 to 110 micrograms per 100 milliliters.[23] Abnormal values are those above 135 micrograms per 100 milliliters. Concentrations between 110 and 135 micrograms per 100 milliliters are in a twilight zone and considered neither normal nor abnormal by us. Figure 1 shows the percentile distribution of various blood ammonia concentrations as determined by our laboratory in 100 normal fasting persons.

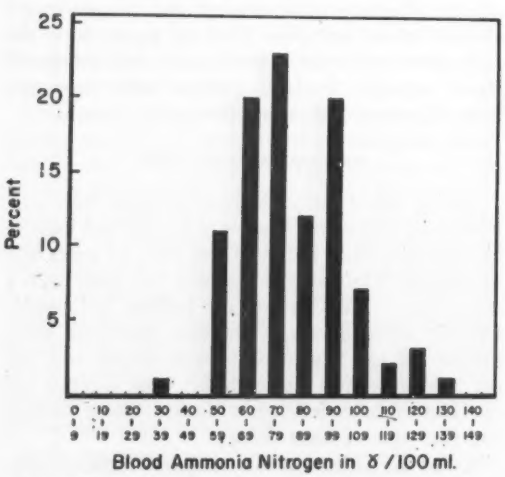

Figure 1. Percentile distribution of various blood ammonia concentrations in 100 normal persons.

RESULTS

Table I lists the blood ammonia concentrations of the patients in this series. It will be noted, out of a total of 29 blood ammonia values, 25 were in the normal range, two were in the twilight range (C. B. and A. M.), and two were markedly elevated (L. F. and R. P.). We were unable to obtain any significant correlation between the blood ammonia concentrations and the size of the liver, duration of congestive failure, height of venous pressure, or degree of abnormality of the standard hepatic function tests.

CASE REPORTS

The clinical courses of the two patients in whom abnormally high blood ammonia levels were found are reported below:

Case 1, L. F., a 35-year-old male, was admitted to

TABLE I

Patient	*Blood Ammonia (micrograms %)*	*Central Nervous System Abnormalities*
O. F.	59	0
E. C.	77	0
V. T.	75	0
J. V.	62	0
D. C.	77	0
C. B.	62, 110	0
L. F.	176	X
I. M.	70	0
L. F.	71	0
T. V.	91	0
A. M.	111, 89	0
F. H.	84	0
G. H.	92	0
M. J.	62	0
M. K.	92	0
F. M.	69	0
G. F.	71	0
W. N.	82	0
C. K.	82	0
J. B.	77	0
S. H.	82	0
M. L.	92	0
G. H.	67	0
H. W.	62	0
L. N.	107	0
R. P.	164, 81	X

the hospital with a diagnosis of subacute bacterial endocarditis due to streptococcus viridans. The patient had had rheumatic fever at the age of 12. He had been asymptomatic until 6 months prior to admission, when he noted fever and fatigue. Three weeks prior to admission he developed signs and symptoms of congestive heart failure.

Physical examination revealed cardiomegaly. Murmurs of mitral stenosis and insufficiency were present. Moist rales were present in both lung bases. The liver was enlarged to 7 cm. below the right costal margin. The spleen was palpable 4 cm. below the left costal margin. Moderate ascites was noted. Two plus sacral, pretibial, and pedal edema was present. Several splinter hemorrhages were noted in the nail beds.

Nonprotein nitrogen was normal. Liver function tests were within normal limits. Blood cultures were positive for streptococcus viridans. Blood ammonia was 62 micrograms per cent.

The patient was digitalized, treated with diuretics, and given eight million units of penicillin daily for six weeks. On this regimen he became afebrile and recompensated. He was discharged on a low salt diet and maintenance gitalin after almost two months of hospitalization.

Seventeen days after being discharged, he was readmitted, acutely ill. For three days prior to this admission the patient had noted lethargy, nausea, vomiting, anorexia, oliguria, and ankle edema.

At this time he was extremely lethargic and apathetic and unable to give a reliable history. No fever was present. The lungs were clear. The cardiac murmurs were unchanged. The liver was enlarged 8 cms. below the right costal margin. Two plus pedal edema was present. Bilateral Babinski signs were noted.

During this hospitalization the blood nonprotein nitrogen rose steadily from 114 to 155 mgm. per cent. The serum sodium ranged from 119 to 132 mEq/L; serum potassium from 7.0 to 7.9 mEq/L., and serum chloride from 89 to 96 mEq/L. Carbon dioxide combining power varied from 8.8 to 15.4 mEq/L. Hepatogram showed a bilirubin of 7.3 mgm. per cent, alkaline phosphatase of 31 millimol units, and cholesterol esters of 11 per cent. Blood cultures were negative. The blood ammonia was 176 micrograms per cent.

The patient was treated with low salt diet, gitalin, and parenteral fluids. Throughout his brief hospitalization, he was restless, confused, drowsy, irritable and hallucinating. During the last 48 hours of his life, he became jaundiced and comatose. He gradually went down hill and died six days after admission to the hospital.

At autopsy the heart weighed 1000 grams. The mitral valve showed an old rheumatic valvulitis with rupture of many chordae tendineae due to healing verrucae. There was dilatation of the right atrium and right ventricle. The left atrium was markedly dilated and contained a mural thrombus. The lungs showed chronic passive congestion. There were tiny healing infarcts in the spleen and kidneys. The liver weighed 1200 grams and showed central necrosis. Tremendous passive congestion was present. In many places the congestion was of such a degree as to simulate hemorrhage in the liver. The sinusoids and liver parenchymal cells were completely overwhelmed by the amount of erythocytes present. It was the conclusion of the pathologist that the superimposed subacute bacterial endocarditis, by further damaging the mitral valve, contributed to congestive failure. It was thought that the endocarditis was healed, but unfortunately the vegetations were not cultured.

During the last few days of this patient's life, he showed many of the signs of a patient in liver failure and coma. He had had no liver disease until congestive heart failure developed. It is reasonable to assume that all the anatomical and functional changes in the patient's liver were due to congestive heart failure. During his first hospitalization, the patient was clear mentally and had a normal blood ammonia level. At the time of his demise he had a markedly elevated blood ammonia level and showed mental and neurological abnormalities.

Case 2, R. P., a 59-year-old man, was admitted to the hospital in congestive heart failure of one month's duration, manifested by dyspnea, orthopnea, and edema. He had had diabetes for 15 years. At the time of admission he was taking 60 units of NPH insulin daily, digitalis, and ammonium chloride.

On admission he was disoriented, lethargic, and repetitious in his conversation. History taking was difficult because of the patient's mental status. Coarse moist rales were present in the right lung base. The heart was not enlarged to percussion, but a grade two apical systolic murmur was present. Minimal ascites was noted. The liver edge was palpable 6 cms. below the right costal margin. Two plus pitting edema of the feet and ankles was present. The hepatogram was normal. The electrocardiogram showed an old anteroseptal myocardial infarction.

The blood ammonia concentration was 164 micrograms per cent on the day following admission. The patient was placed on a 1700 calorie rice and fruit diet that contained 50 mgm. of sodium a day. He was given 20 units of NPH insulin and 0.15 mgm. of digitoxin daily. His weight dropped from 160 to 139 pounds, and his dyspnea, orthopnea, and edema disappeared. For the first few days in the hospital, his sensorium remained unchanged. Then

it gradually became clearer as his congestive failure was controlled. On the day of his discharge from the hospital, he was mentally alert and fully oriented. A repeat blood ammonia level at that time was 81 micrograms per cent.

This patient showed an abnormally high blood ammonia level associated with mental aberrations and cardiac decompensation with passive congestion of the liver. As he responded to treatment, his liver became smaller, the blood ammonia level returned to normal, and he became mentally alert again. It is interesting to speculate on the role of the ammonia chloride that he received prior to admission in the production of a high blood ammonia level in this patient. Hepatic coma has been produced in patients with liver disease by the administration of ammonia chloride.[24]

The following case report is not included in our series because it represents a patient who had Laennec's cirrhosis in whom congestive heart failure had developed. However, it is reported in detail because it is illustrative of the mental and neurological changes that may occur when congestive heart failure is superimposed on a previously damaged liver.

Case 3, J. P., a 49-year-old white male, was seen in the outpatient department complaining of shortness of breath. For two years he had noted dyspnea which had become progressively worse in the preceding two months. He gave a history of pedal edema of five months duration and abdominal swelling of two months duration with a weight gain of 50 pounds during the latter period. He had been in good health prior to his present illness but had consumed several pints of whiskey weekly for 15 years previously.

Physical examination revealed a well developed, obese (287 pounds), white male in moderate respiratory distress with generalized anasarca. Blood pressure was 150/90, pulse 92, and respirations 32. Generalized high pitched musical rales were heard throughout the chest with moist rales in both bases. Cardiac dullness could not be percussed accurately. Heart tones were distant. No murmurs were heard. The abdomen was protuberant, and a fluid wave was present. The liver was enlarged 8 centimeters below the right costal margin, was nontender and finely nodular. There was marked pitting edema of the lower extremities up to the level of the second lumbar vertebra.

A diagnosis of Laennec's cirrhosis was made, and the patient was admitted to the hospital for further treatment. On admission nonprotein nitrogen and serum electrolytes were within normal limits. Hepatogram revealed the following values: Total bilirubin 1.5 mgm. per cent, alkaline phosphatase 2.4 millimol units, thymol turbidity 13 units, cephalin cholesterol flocculation 2+ in 48 hours, total cholesterol 242 mgm. per cent with 41 per cent esters, prothrombin concentration 75 per cent. Blood ammonia concentrations on the second and third hospital days were 147 and 170 micrograms per cent respectively. The electrocardiogram showed sinus tachycardia, left axis deviation, and abnormal T waves. A chest x-ray showed the heart size as at the upper limits of normal.

The patient was treated with bed rest, low salt diet, digitoxin, and aminophylline. On the tenth hospital day he became lethargic and developed increasing dyspnea and cyanosis. A chest x-ray at this time showed pulmonary congestion and cardiomegaly. Paracentesis was performed with some relief of symptoms.

On the 14th day the patient began hallucinating and became disoriented and confused. It was felt that he was in the precoma stage of hepatic coma. However, a blood ammonia level at this time was 120 micrograms per cent. He was started on cortisone in a dosage of 75 mgm. a day. Mental confusion continued intermittently.

On the 22nd day the patient developed dyspnea and deep cyanosis. His confusion and delirium increased. It then became apparent that the degree of heart failure had been grossly underestimated. Death was expected momentarily. Paracentesis and phlebotomy were performed as emergency measures. Dyspnea and cyanosis improved, but the patient developed typical hepatic coma which lasted three days. During this period blood ammonia levels were 211, 150, and 231 micrograms per cent. In an effort to alleviate the coma, a total of 69 grams of monosodium glutamate was given intravenously over a three-day period.

By the 27th day his sensorium had cleared, his weight had dropped to 220 pounds, and he was able to be up and around. Chest x-ray at that time revealed that the transverse diameter of the cardiac silhouette had decreased by two and one-half centimeters. From that time on the patient steadily improved and responded well to diuretics. Liver biopsy was done on the 52nd day and demonstrated diffuse hepatic fibrosis and fatty metamorphosis. He was discharged on the 53rd day on a low salt diet and a maintenance dose of digitoxin. At the time of discharge he had no edema and only a trace of ascites. However, his liver was still enlarged eight centimeters below the right costal margin. The blood ammonia level was 159 micrograms per cent at this time. Seen in the outpatient department two months later, the patient weighed 200 pounds and had no edema or ascites.

This patient illustrates some of the profound metabolic changes that may occur in a patient with a damaged liver who develops congestive heart failure.

These changes, reflected in mental and neurological abnormalities and elevation of the blood ammonia concentration, were successfully handled only by vigorous treatment of the heart failure simultaneously with efforts to relieve portal systemic encephalopathy. Here a combination of systemic diseases—hypertensive cardiovascular disease and Laennec's cirrhosis—found in the same patient serves to illustrate and bridge the discussion from the first two cases of primary heart disease and the third case of primary liver disease.

DISCUSSION

In view of the autopsy findings, it seems obvious that the cause of death in the first case was severe congestive heart failure. The severe degree of congestion of the liver was sufficient to result in a marked degree of jaundice as well as to cause abnormalities in the standard liver function tests. The abnormally high blood ammonia demonstrated in this patient can best be explained by the severe degree of hepatic damage. It is postulated that some of the high ammonia containing portal vein blood was shunted around the liver and directly into the systemic circulation as a result of the tremendously increased intrahepatic pressure.

In addition, the surviving hepatic cells were probably unable to synthesize urea from ammonia because of damage to them as a result of high intravascular pressure and hypoxia within the liver. We are unable to satisfactorily explain the azotemia in the patient. Possibly it may have been the result of renal dysfunction, secondary to severe chronic passive congestion and hypoxia.

The second case illustrates a correlation between congestive heart failure, elevated blood ammonia level, and mental aberrations. Again we wish to emphasize that an elevated blood ammonia level is only one metabolic abnormality in a complex picture. Any attempt to explain the mental or neurological picture of hepatic coma on the basis of an elevated blood ammonia alone is a gross oversimplification. Numerous other metabolic abnormalities are undoubtedly present.

The third patient showed an elevated blood ammonia level associated with mental and neurological changes. Two factors seem to be instrumental in the production of this picture. It is postulated that this patient already had a severely damaged liver due to cirrhosis. When he developed congestive heart failure, further damage was inflicted on the already malfunctioning liver, and consequently the blood ammonia concentration increased and the patient developed typical hepatic coma. Only prompt energetic treatment of the congestive failure kept this patient from dying in hepatic coma. Just how great a part each factor played in the production of hepatic coma in this patient can only be surmised. The role of monosodium glutamate in this patient's rapid recovery is unknown. Theoretically, sodium glutamate is supposed to lower the blood ammonia level by combining with ammonia to form glutamine and thus free more alpha keto glutarate to take part in the Krebs cycle in the central nervous system.

Since it has been shown repeatedly that the administration of Diamox, ammonium chloride, and cation exchange resins in hepatic disease may cause an elevation of the blood ammonia level, it becomes obvious that these therapeutic agents may be containdicated in severe chronic passive congestion of the liver. It seems apparent from clinical studies that an elevation of the blood ammonia is associated with definite neurological and mental signs and symptoms.

It is apparent from the results of this study that a great many patients with congestive heart failure and chronic passive congestion of the liver have normal blood ammonia levels. Since Diamox, ammonium chloride, and cation exchange resins have been used repeatedly in the routine treatment of congestive failure without detrimental effects, it seems reasonable to assume that in the average case they are relatively innocuous. However, if a patient in congestive failure shows a severe degree of hepatic congestion and/or mental or neurological aberrations, the administration of any of these agents which are known to be able to precipitate hepatic coma is contraindicated. In brief, it is to be emphasized that the indiscriminate use of ammonium chloride, Diamox, and cation exchange resins in congestive heart failure is to be condemned. While the use of these agents is beneficial in most patients, it may well be detrimental in some.

Additional studies of blood ammonia levels in patients with congestive heart failure before and after the administration of Diamox, ammonium chloride, and cation exchange resins are contemplated. The use of the ammonium chloride tolerance test as described by White and others[24] in patients with liver disease would be of interest in this group of patients. The role of antibiotics in lowering an abnormally high blood ammonia, by decreasing the amount of amine forming bacterial flora in the intestinal tract, needs to be evaluated. The part played by electrolyte imbalance in congestive heart failure in relation to mental and neurological changes requires further investigation.

SUMMARY

1. Blood ammonia levels were determined in 26 patients with congestive heart failure and hepatomegaly. A total of 29 determinations were performed,

of which 25 were normal, two borderline, and two markedly elevated.

2. The clinical courses of three patients with elevated blood ammonia levels are reported. These patients exhibited mental and neurological abnormalities similar to those found in patients in hepatic coma. To further the correlation, one case report deals with a patient who had Laennec's cirrhosis and subsequently developed congestive heart failure and hepatic coma.

3. Possible explanations for elevated blood ammonia levels in congestive heart failure are discussed.

4. The potential hazards involved in the use of Diamox, ammonium chloride, and cation exchange resins in patients with congestive heart failure and hepatic damage are emphasized.

5. The need for additional investigative studies in this field is brought out.

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Every day increases the sheer weight of knowledge put into our hands, some new power control over natural processes. . . . Our age is being forcibly reminded that knowledge is no substitute for wisdom. Far and away the most important thing in human life is living it.

—Rt. Rev. F. R. Barry

Biopsy

Panel Discussion on Its Role in the Spread of Cancer

Moderator: **DAVID W. ROBINSON, M.D.,** ***Kansas City***

Participants: **ARTHUR DeBOER, M.D.,** ***Chicago***
WILLIAM T. FITTS, JR., M.D., ***Philadelphia***
VICTOR F. MARSHALL, M.D., ***New York***
JOHN R. McDONALD, M.D., ***Rochester, Minnesota***
JOHN R. PAINE, M.D., ***Buffalo***

Dr. Robinson: Our conference committee thought that we might profitably discuss in this day devoted chiefly to cancer some of the indications for biopsies in various parts of the body and some of the definite contraindications wherein a biopsy might cause more harm to the patient than had the biopsy not been done. I am sure you will all agree that the first stated objective is the correct one. When in doubt, a biopsy to establish what is wrong, so that we can decide what to do, should be our chief conclusion.

The first question to come up before our panel is whether biopsies can make some difficulties for us. Because of the experience I have had with some of these, I would like to ask the opinion of some of the gentlemen here what their experience has been. First, and the most difficulty I have had about doing biopsies, at times, relates to melanomas. I would like to start by asking Dr. McDonald if he'd say a word of what he thinks about biopsies of melanomas. Can we ever get in trouble by biopsying, let's say, a lymph node that has melanoma in it and that might make future troubles for us?

Dr. McDonald: I do not know about the potential danger of biopsy of a lymph node containing a melanoma. However, melanotic lesions of the skin should not be treated by cautery without biopsy, as is occasionally done. Under such circumstances it is not unusual for melanotic lesions to be thrown away without histologic study, only to have a metastatic tumor appear subsequently in a lymph node. I believe that biopsy of a melanotic lesion in the skin usually should include excision of the lesion. Incisional biopsy of such tumors should be avoided if possible.

Dr. Robinson: I think that's a significant point. Dr. DeBoer, how wide do you think excisional biopsy should be with a suspected melanoma? What has been your practice?

Dr. DeBoer: That follows the line of the discussion this morning. I exposed my conservatism then, so I'll reaffirm it just a bit. The pigmented lesions that we see in children, of course, are the things that we have in mind. The first question is, "Is this a junctional cell nevus which later on may prove to be malignant or at least take on malignant aspects?" We excise all those; we excise very conservatively in the respect that we make sure that we have a rim of normal tissue that you can see with the naked eye and not have the pathologist only hope that he can find some normal skin microscopically—you can see normal skin around the entire border of the pigmented lesion. Then, the incision is carried down through the subcutaneous fat, but the underlying fascia is not excised. These are the usual excisional biopsies that we do on all the pigmented lesions in children.

This discussion was presented at the University of Kansas Medical Center, Kansas City, January 17, 1956, as part of the 11th Annual Postgraduate Course in Surgery.

Dr. Robinson: Does the age of the child make any difference in your consideration of these nevi?

Dr. DeBoer: We used to feel rather sure that if we got the child before puberty we didn't have to worry. We have changed our minds recently. We like to have the pigmented lesions excised at four, five, and six years rather than waiting until they are nine, ten, and eleven years because of the variation in the physiology of puberty in various children.

Again, if it were a suspicious looking lesion on the palm or the sole of the foot, which we know are

not particularly fortunate places to have one, and if the child were 11 or 12 years of age, yes, I would excise that a little bit more widely than I would on a two-year-old baby with a pigmented lesion on its abdomen, for example.

Dr. Robinson: Now we bring up this subject because we have seen an instance or two wherein regional nodes have become enlarged. We have no antecedent history of the removal of a mole obtainable; or, if we have a history of removal, we do not know whether or not it was malignant. Maybe it's been thrown away, which I urge you never to do. And this node is enlarged in the neck or in some other regional lymph node area following the removal of a nevus. We have seen where a needle has been inserted into a node to try to get a needle biopsy to determine what might be the cause of the lymphadenopathy. I'd like to show the first slide on melanoma. Dr. Boley obtained this slide for us from his friend down at Columbia, Missouri, Dr. Richard Johnson.

Dr. Boley: You can see the needle track in the tissues. It goes down and has punctured the node. Under higher magnification you will find that in each one of these fascial planes there is melanoma growing out in either direction and along the track so that, if one decides to do this sort of procedure, he has to be willing to proceed farther and remove those needle tracks. If you come from several directions toward the node in doing the needle biopsy, you will sacrifice as much skin as with the definitive operation contemplated.

Dr. Robinson: Thank you, Dr. Boley. Needle biopsies are done frequently in some institutions. Here's one instance where I think one can say that there's been trouble from a needle biopsy, and I would like to ask these gentlemen how they feel about needle biopsies for informational purposes in general. Dr. McDonald, do you employ this very much in your institution?

Dr. McDonald: The surgeons at my institution use needle biopsy for very specific indications. They would not use this procedure in a situation such as the one just described because they believe that one should be able to excise the sinus tract whenever needle biopsy is used if the lesion proves to be malignant, because implantation along sinus tracts can occur. Needle biopsy is of greatest value in situations such as that of the patient who has a lesion that is obviously malignant and not removable. I think it may be used best in a situation when such a procedure might save the patient undergoing anesthesia and an operation, with a fairly long stay in the hospital. Needle biopsy of the liver is of particular diagnostic value. Thus, I would not condemn needle biopsy as of no value, but I certainly agree with what Dr. Boley has said and Dr. Robinson has advised. Needle biopsy should be used with some care.

Another factor is that the average pathologist may not know how to interpret material obtained by needle biopsy. He is handicapped if he is not experienced with this procedure. Needle biopsy may be done by several methods. One way is to macerate the material on a slide and make a smear; this is the technic used at Memorial Hospital. In other places, a bore of tissue is taken, which is the procedure that my associates and I have used.

Needle biopsy may be of great importance in making a diagnosis of deep-seated pancreatic lesions. With the abdomen open, one may do a needle biopsy of the pancreas because it is sometimes impossible to excise tissue containing malignant cells in carcinoma of the pancreas. Approximately 15 per cent of gross diagnoses of pancreatic carcinoma based on firmness of the involved tissue are erroneous. Thus, before a radical operation is done on the head of the pancreas for carcinoma, it is essential to have a histologic diagnosis. Needle biopsy from deep in the pancreas and study of the tissue so obtained by rapid frozen section will answer this problem and be of considerable help to the surgeon.

Dr. Robinson: Dr. Paine, do you employ needle biopsies very much in your institution or does your staff?

Dr. Paine: In my institution needle biopsies are almost entirely confined to the medical wards. The internists do them but the surgeons rarely. Dr. McDonald has touched on the point that has disturbed me most about needle biopsies, or rather the thing about biopsies that has bothered me most, and that has to do with the business of pancreatic lesions. I can see where he well may be right in advocating the use of needle biopsies in the head of the pancreas. On the other hand, there's another phase to this problem, and that is to utilize the needle biopsy for its best value. You've got to have the cooperation of the pathology department. Now Dr. McDonald is a very cooperative pathologist. He's almost a surgeon, but he hasn't got a knife. You can find many pathologists who will discourage you from using needle biopsies, and they will go to great lengths to tell you that they're valueless. Well, who am I to say that they aren't telling me the absolute truth? We have been discouraged somewhat about attempting to use needle biopsies.

Then there's another point that hasn't been brought up yet, I think, and that is that the positive evidence that you may get from a needle biopsy is very valuable, but the negative evidence doesn't mean so much. In other words, can we always be positive that we're getting this tissue from the place we would like to

have it? What do you think about that, Dr. McDonald?

Dr. McDonald: I agree wholeheartedly, Dr. Paine, that negative results of biopsy are not of much diagnostic value.

Dr. Robinson: Don't you think there needs to be some education amongst you pathologists about the proper utilization of this method?

Dr. McDonald: I think so. As already indicated, some pathologists have not been trained in the method. It is probably not wise to force a pathologist to use a technique with which he is unfamiliar.

Dr. Robinson: That, then, will narrow the possibilities of utilizing any procedure really to the capabilities of one's own staff. When you have a pathology department that refuses to make a diagnosis on a needle biopsy, I think you'll just have to give it up. Dr. Marshall, you have use for needle biopsy, don't you, in your field of endeavor at times?

Dr. Marshall: We have some use for it. While these gentlemen were talking there came to my mind a specific example about the lack of *exclusive* value that an aspiration biopsy has. Consider the circumstance of an apparently operable prostatic carcinoma. If one aspirates a lump in the prostate and demonstrates carcinoma, he operates because it's carcinoma (conditions permitting, of course). If he aspirates it and doesn't get carcinoma, he operates to see why he didn't get carcinoma.

I think that's an entirely different matter, however, from the patient who already has metastases and a big hard prostate. This prostate is much easier to aspirate successfully, and the surgeon can have perfectly concrete evidence of carcinoma of the prostate before the patient is deprived of his orchids. It is possible, however, to implant carcinoma along the aspiration line; but considering the diffuseness of the disease already, this consideration does not assume much practical significance.

I would like to add one other thing, if I might, about this business of the pathologist. When I first went to Memorial Hospital, I didn't think the pathologist's reports from aspiration meant much, but I changed my mind drastically. It is actually quite valuable as long as you know that a positive report nearly always means cancer, but a negative report is of little value to indicate that cancer is absent. Many aspirations are done at Memorial, so their pathologists not only have much interest and large experience, but also constant practice. It makes a lot of difference who the pathologist is.

Dr. Robinson: That brings us to a point which may be heresy to say before a pathologist. But I think they will agree also with us that there are times wherein may be they've erred a bit. When one goes too positively on the histological diagnosis as against his clinical judgment, I'm sure he's going to cause some havoc at times if the clinical judgment is good. If it's bad, of course most anything might happen.

I had a patient we worried about quite a lot. He had a large golfball size mass in his left tonsil and a big mass in his neck. We had the tonsil removed, and we took out a node in the neck, thinking this was a lymphoma. All we could come up with was hypertrophy of lymph node, and that's all. But clinically it was lymphoma. So the patient was treated, properly, with radiation after about the third biopsy, which still looked like hypertrophied lymph node. The lymphatic tissue completely regressed. At least it has for a couple of years, and what comes later we don't know. But there are instances, I am sure, wherein we can be misled by the biopsies. Would you agree with that, Dr. McDonald?

Dr. McDonald: Yes, I agree. I should like to make one other point if I may. It is a well known fact that an inexperienced resident may be able to obtain positive results in 60 per cent of carcinomas of the breast by means of needle biopsy. As he becomes better and more adept at the procedure, it is possible to obtain positive results in 80 per cent of such cases. Perhaps part of the reason for a high incidence of negative results is that the problem of aspiration biopsy may be turned over to the greenest man on the staff.

Dr. Marshall: Sometimes we "ripe" surgeons are not so good ourselves! I've tried to aspirate many little lumps in the prostate without success; and then explore, take the regular biopsy, and find out that it is carcinoma. That's one reason why I don't frequently put needles in the prostate. But it's amazing how adept some persons can get at hitting things with a needle. Simple practice makes for much improvement. And it's amazing that they get into so little trouble.

Somebody mentioned aspirating the liver here a minute ago. I saw an example of a liver aspiration in which two holes were also made in the gallbladder!

Dr. Robinson: Dr. McDonald mentioned a moment ago about carcinoma of the breast, and herein I think our treatment is directed definitely according to what biopsy findings are at times. Dr. Fitts, have you some thoughts about biopsy of the breast and how it directs your treatment?

Dr. Fitts: We almost routinely do biopsy of the breast, Dr. Robinson, and in our hospital at the University of Pennsylvania almost never do aspiration biopsies of breast lumps. When I was a resident, a woman was presented at a tumor conference who had an extensive lesion in the breast with all the classical signs of cancer. The two men with the most experience with breast cancer at our hospital said, "It's ridiculous to biopsy this breast. Go right ahead

with a radical mastectomy." I went ahead with radical mastectomy, and pathological examination showed only extensive chronic cystic mastitis with inflammation. This experience has stayed with me. I feel that, although I'm sure I'm right in most instances of very definite cancer, I ought to make a completely definite diagnosis. I believe it would be almost impossible to prove clinically that a biopsy of a breast lesion has worsened the prognosis to any extent. We are fortunate in most breast lesions that we can tell the diagnosis at the time of the operation and go ahead with the proper operation. In my experience, in all but about 2 or 3 per cent of breast lesions, a gross and frozen section diagnosis at the time of operation has been definite and correct and we have gone ahead with radical mastectomy if cancer were present.

On the other hand, if there is reason to doubt that the lesion is malignant, we do not believe that waiting until a paraffin section is available, 36 hours or two days, really materially alters the prognosis, and we think it's valuable to wait. In our experience it's been especially the peripheral papillary type of lesion in the breast that has been hard to tell by a frozen section examination.

Dr. Robinson: What precaution do you take in doing a biopsy of the breast and then proceeding with a mastectomy not to seed the field?

Dr. Fitts: There's no question, Dr. Robinson. It's been shown many times that the instruments used for biopsy may transmit viable tumor cells; all instruments used for biopsy should be discarded and the wound completely draped before radical mastectomy is begun.

Dr. Paine: Excuse me. Do you close the wound or pack it?

Dr. Fitts: We close it, but I sew a piece of gauze over the wound so that no blood will seep out of the wound following biopsy. In small lesions we almost routinely do an excision of a breast lesion. In large lesions we may do an incision biopsy.

Dr. Robinson: Dr. Paine, it seems to me that the thyroid is a site which lends itself at times to considerable discussion as to what to do about a nodule in the gland. Certainly you have to explore it. We're all agreed about that. What is your procedure in investigating a nodule in the thyroid, and how do you go about it?

Dr. Paine: If a patient is being operated upon, we take out the nodule, and I can't conceive of our sticking a needle in it before operating on it, although that might be the proper thing. We wouldn't. We would remove the nodule surgically and then I think we'd be arguing in some instances for the next two weeks whether it was cancer or not. That's not true in every case, of course. But I would feel that wherever possible a lesion in question should be excised rather than incised or have a needle stuck in it, and I would try to follow that general principle in dealing with thyroid nodules.

Dr. Marshall: Dr. Paine, if a nodule in the thyroid involves a good part of the lobe, would you go ahead with a clean thyroidectomy, removal of the isthmus, at that time so that, let's say, if this were malignant, it wouldn't need a secondary operation? Or would you feel that you need more if this were malignant?

Dr. Paine: I would probably trust my surgical judgment and in some instances would probably proceed with a hemithyroidectomy and hope I'd be borne out later on by the pathological study. I can conceive, though, of instances where I might do either. I think that's a very difficult field in which to make a dogmatic statement.

Dr. Robinson: Isn't it true, gentlemen, and I'd like Dr. McDonald especially to answer this, that some metastasizing carcinomas of the thyroid look quite histologically benign? In bones or lungs they look just as benign as can be. Isn't that right, Dr. McDonald?

Dr. McDonald: Yes, that's right, Dr. Robinson. Dr. Paine has brought up an extremely interesting question. A pathologist who does many frozen sections becomes adept at them, but a small number of thyroidal cancers still exist, particularly the solid type of thyroidal cancer, that give diagnostic difficulties when studied by means of fresh frozen sections. Occasionally a final opinion cannot be given without study of fixed sections.

Dr. Robinson: Isn't it better to take out those nodules?

Dr. McDonald: I think so.

Dr. Robinson: In toto?

Dr. McDonald: Yes, in toto. What's more, most nodules that are questionably malignant on fresh frozen section are found to be carcinomas in the final analysis. Of course it is relatively easy to diagnose the papillary group of lesions by means of fresh frozen sections. I believe that rapid frozen-section diagnosis of thyroidal malignant lesions is of value as a guide to further surgical procedures.

Dr. Robinson: Then the positive evidence that you can get at the table is very valuable, but negative evidence isn't?

Dr. McDonald: No, it is not.

Dr. Robinson: We are always faced with that in so many fields of surgery. Now, there are other instances in which tissue looks histologically benign, but actually it's clinically malignant and it has infiltrative characteristics. Is this not true, Dr. McDonald?

Dr. McDonald: Oh, yes.

Dr. Robinson: For instance, carcinoma of the mouth.

Dr. McDonald: The histologic diagnosis of squamous cell carcinoma of the floor of the mouth may

be extremely difficult. In particular, it is difficult to differentiate papillary squamous cell carcinoma of the floor of the mouth from benign papillary hyperplasia. Most of these lesions are malignant clinically and yet they look benign microscopically. Another region that poses problems is the prostate. Slowly growing, gland-forming cancers of the prostate raise difficult diagnostic problems for the pathologist. Tissue obtained from the prostate by perineal biopsy should be diagnosed without delay because it is best for the surgeon to proceed with definitive surgical therapy immediately rather than to reopen the operative field later.

Dr. Marshall: Yes, I think that's true. What Dr. McDonald said has a lot to do with the reported cure rates in carcinoma of the prostate too. What some people call carcinoma of the prostate is not what some other people agree to.

Dr. Robinson: Well, now, to change the field of endeavor a little bit. Dr. DeBoer, what about the large tumors in the flank of children? Is it necessary to biopsy them to make a diagnosis?

Dr. DeBoer: I presume you're referring to the Wilm's tumor or neuroblastoma in general. No, about the only time we are concerned about the diagnosis is in an invasive type of tumor and we're wondering whether or not it is of the lower grade malignancy, such as was intimated in the neuroblastoma. We may ask the pathologist to further identify it. Say, for example, the tumor is invasive into the chest wall or posterior peritoneal wall. If it's a sarcomatous lesion, I think it's hopeless if it's invaded into the area of the inferior vena cava and the aorta. Whereas, if it's a neuroblastoma, we feel very encouraged in spending another hour and trying to get practically all the tumor out. Even though all of the tumor is not removed, we feel we get considerably better results if we get most of the tumor out followed by x-rays. Whereas, if it's a sarcoma, I think it would be rather ridiculous to risk sacrificing the youngster's life with a tumor that is already far beyond the limits of surgical excision.

Dr. Robinson: Then you proceed with exploration without knowing the exact site in this instance?

Dr. DeBoer: If it's a tumor that we find, for example, on the posterior peritoneal wall that has invaded, and we feel it's going to be exceedingly difficult to remove, we may very well take a specimen of the tumor and send it over to the pathologist. If he can tell, for example, that it is a sarcoma, I think we would be less energetic in trying to get it because it has already invaded so far that surgical excision would probably not be feasible. In the more benign type of tumors, such as the neuroblastomas, we would be more energetic in removing them.

Dr. Robinson: Let's change the subject once more. Here's one that strikes me right in the middle of my solar plexus at certain times. That is what to do about the parotid tumor. The pathologist may not be able to help me, and I may not be able to tell, and I sweat away for two hours to avoid having some old guy going around afterward with his face all drooping down and have him say, "Well, I'm Dr. Robinson's patient. Look what he did to me." Yet, of course, if it's carcinoma, we should be just as radical as possible because these are very malignant tumors at times, and they could do away with the patient. Certainly there is a high recurrence rate. And yet we know that if we break the capsule of the parotid and even though it's only a mixed tumor, there's a good chance that we'll seed some area that may lie dormant for two or three years and then come back. Dr. McDonald, do you have any thoughts on biopsy of parotids in the management of a tumor?

Dr. McDonald: The best way to handle parotid tumors is to take material for biopsy and make fresh frozen sections immediately. It is possible for the pathologist to arrive at the correct diagnosis in almost every instance. For instance, it is relatively easy to recognize cylindromas if one has seen a few of them. Mixed tumors, of course, comprise 70 per cent of tumors of the parotid and usually can be recognized with certainty. All one is interested in at the operating table is whether the lesion is benign, which usually means that it is a mixed tumor, or whether it is malignant. The particular type of malignancy is not necessarily important at that time because treatment should be decided, if possible, right then and there. The parotid gland is one of the regions of the body in which the employment of fresh frozen sections is of greatest value.

Dr. Robinson: How about lymph nodes for fresh frozen sections?

Dr. McDonald: The accurate histologic diagnosis of lymphoma in fresh frozen sections is extremely difficult. However, other diseases of lymph nodes can be recognized with relative ease. For instance, it is easy to diagnose Boeck's sarcoid and carcinoma in fresh frozen sections of lymph nodes.

Dr. Robinson: Of course for the most part it doesn't affect the treatment very greatly anyway, does it? But some of these others do affect the treatment. Now we run into instances where carcinoma has been incarcerated in scar tissue, or irradiated tissue, for quite a long period of time, maybe in cervical nodes or about the face, and we're rather wary here of doing a biopsy at times because we've seen instances in which the tumor, having had its growth and energy held back for a long time, gets loose and goes like wildfire. Have any of you gentlemen had experience with this type of thing in the neck?

Dr. DeBoer: We have. Where they've been heavily radiated, they will just get loose after a biopsy and go wild. We're afraid to do them.

Dr. Paine: Don't you think they do it without biopsying sometimes?

Dr. Robinson: Oh, yes, certainly they can.

Dr. Paine: Are you sure that biopsy causes it?

Dr. Robinson: No, we're not positive. It just follows and certain cause and effect seem to be present.

Dr. Robinson: We don't want to prolong this too long. There may be questions from you that you'd like to propound to these gentlemen. I have one here before me written out. What is the incidence of ovarian involvement with carcinoma of the breast? Will you answer that, Dr. Fitts?

Dr. Fitts: In an autopsy series that we've just gone over—a consecutive series of patients who have died of metastases from carcinoma of the breast—we found the ovaries involved in almost 20 per cent. The thing that has interested us in a group in whom we have done prophylactic oophorectomies is that we found a number of ovaries containing metastases not suspected before operation. I think we found actually about 10 or 15 per cent. In some the metastasis was not recognized until the ovary was sectioned.

Dr. Robinson: Dr. Fitts, if it's true that 20 per cent of autopsy cases have involvement of the ovaries, then isn't it almost a necessity to do a bilateral oophorectomy in every patient with carcinoma of the breast?

Dr. Fitts: We believe it is if distant metastases are present.

Dr. Robinson: Do you know of any other series anywhere near that high?

Dr. McDonald: Were the ovaries you studied obtained from patients who had generalized metastasis?

Dr. Fitts: First, we went over all the patients who had autopsies who had died of carcinoma of the breast. I have forgotten the exact percentages of metastases to the ovaries, but I think it was almost 20 per cent. One would expect a high percentage because these patients died with widely disseminated disease. These were autopsy cases. But we were interested especially in four or five patients in whom at prophylactic oophorectomy (with no evidence of distant metastases), we found small foci of carcinoma in the ovaries on section. This finding may not hold up in a larger series.

Dr. Robinson: Now the other half of this question, Dr. Fitts, is: When the ovary is involved, does it affect the prognosis?

Dr. Fitts: I can't answer that. We wondered about it. People talk about spontaneous regression of tumors. We wondered if possibly some of the reported cases of spontaneous regression of breast carcinoma might not be due to destruction of the ovary by metastases.

Dr. Robinson: I remember Danely Slaughter discussed a patient of his who had had extensive adrenal metastases with replacement of adrenal tissue by carcinoma from the breast and who was in a state of remission for a long period of time.

Dr. Fitts: We also wondered if some of these spontaneous cancer remissions might not be due to metastases to endocrine glands.

Dr. Robinson: Another question. Some of the surgical literature recommends in parotid tumors to split the gland and save the seventh nerve. In view of Dr. McDonald's statement about cylindromas metastasizing along the lymph channels, by the nerve, would he recommend saving the seventh nerve in this instance?

Dr. McDonald: I believe that total parotidectomy with sacrifice of the seventh cranial nerve is necessary to cure a cylindroma of the parotid gland.

Dr. Robinson: And hasn't it also been your experience that some of these are real sleepers, that nothing happens for a while, and then all of a sudden something does happen in three or four years?

Dr. McDonald: Yes, an amazing number of people who have been treated surgically for cylindroma have remained free of symptoms for five years, and yet they are not cured. We just do not cure them.

Dr. Robinson: I recently had one of the submaxillary gland that went 12 years, and then had bad troubles with generalized metastases.

The next question asked here: Dr. McDonald, there is a small clinic in Ohio which has reported a spread of cancer up the inferior mesenteric vein when cancer of the rectum or sigmoid is manipulated. Could this happen from a rectal biopsy for carcinoma?

Dr. McDonald: That small clinic isn't so small; it happens to be the Cleveland Clinic. Malignant cells were found in the blood in some cases in which venous blood was centrifuged and subjected to cytologic studies. Manipulation presumably forced the malignant cells into the venous channels.

Dr. Robinson: The next question: Would you ever biopsy through a lesion on an extremity which was suspiciously brown-black? Who would like to answer that?

Dr. Fitts: The answer to that is "No," in my opinion. I think it should be excised with a wide margin of normal skin.

Dr. Robinson: Now suppose it was a large lesion that was suspicious and one had a coverage problem afterward. I suppose then you'd take it off anyway and cover it the best you could, cutting it widely around the side.

Dr. Fitts: I think so. You have had more experience with this problem than I.

Dr. Robinson: Well, that's the way we'd manage it. And yet, if it's going to affect treatment (and I think this is true of biopsy in general, to have the prior knowledge), I wouldn't feel remiss to take a

small section at the edge and find out what it is. It could make a great difference in the type of treatment thereafter.

Dr. Fitts: The lesion suspicious of being a malignant melanoma would worry you more than any other type, would it not?

Dr. Robinson: Yes, that's true. The other part of this question is: How would you biopsy the above case with a large axillary mass and with a suspicious lesion on the fifth finger? How would you biopsy this same lesion if you had a large mass in the axilla, the lesion being primary on the finger?

Dr. Fitts: I think you'd want to know what the primary lesion was. I would biopsy the finger lesion. That's one of those instances where you'd want positive information.

Dr. Robinson: There is one other question which I think Dr. Marshall could answer and we'll terminate our discussion. Do you, Dr. Marshall, do punch or transurethral biopsies of the prostate for nodular prostate?

Dr. Marshall: It all depends on whether I think a man is curable by a radical prostatectomy. If he is curable by a radical prostatectomy and operation is feasible, then I suppose the thing to do is expose the area (I prefer the perineal approach), take out the lump, do a frozen section, and proceed. If he is not operable that way, then I would probably do it transurethrally.

Dr. Robinson: Thank you very much. And we thank the members of our panel for this very pleasant session.

Cardiovascular Laboratory

Report of Activities at University of Kansas Medical Center, May, 1953, to May, 1955.

E. GREY DIMOND, M.D., ***Kansas City***

A report from this unit was published in the JOURNAL OF THE KANSAS MEDICAL SOCIETY in November, 1953. In that report the activities of the first two years of operation of the Cardiovascular Laboratory at the University of Kansas Medical Center were described. This present report summarizes the second two years, from May, 1953 to May, 1955.

This review is divided into six sections:

I. Personnel, Residents, Fellows, and Visiting Professors.
II. Clinics, Consultations and Hospital Services.
III. Publications, Exhibits, Postgraduate Courses and Research.
IV. Diagnostic Procedures.
V. Surgical Procedures.
VI. Grants.

I. PERSONNEL, RESIDENTS, FELLOWS, VISITING PROFESSORS AND VISITORS

A. *Personnel*: The clinical staff of the laboratory has continued to be Dr. T. K. Lin and Dr. E. Grey Dimond.

Dr. Kurt R. Reissmann has continued his work as chief of the Experimental Medicine Section.

Dr. Dimond is professor and chairman of the Department of Medicine and director of the Cardiovascular Laboratory.

Two additional staff physicians have joined the group. Dr. Santiago Grisolia activated the Enzyme Chemistry Unit in April, 1954, and Dr. George Curran transferred his work on cholesterol metabolism to the campus in August, 1954. These two men, each an Established Investigator of the American Heart Association, have been major additions. They, with Dr. Kurt Reissmann, have the responsibility for the major basic research activities of the laboratory.

Other physicians, while not members of the cardiovascular laboratories, have had major roles in cardiovascular work at the Medical Center. Dr. Robert Jordan of the Department of Medicine has directed the peripheral vascular studies. Dr. Frank Allbritten, Dr. Creighton Hardin, and Dr. C. Frederick Kittle, of the Department of Surgery, have been cardiovascular surgeons. Dr. Antoni M. Diehl, of the Department of Pediatrics, has seen a considerable share of the pediatric heart work. These men have, in addition, carried on their own investigative programs.

The second two years of operation of the Cardiovascular Laboratory at the University of Kansas Medical Center ended in May of this year. This report summarizes activities of that unit.

The secretarial staff, responsible for the administration of the laboratory, has been Miss Kathryn Calderwood, executive secretary, and Mrs. Eleanor Lane.

B. *Residents*: Several physicians have received training in the field of cardiovascular diseases during this two-year period. The residents in medicine have continued to have tenures of four months each on the cardiovascular service. In this period, Doctors Gustave Eisemann, Chesterfield G. Gunn, Frances Allen, Arnold Greenhouse, Marcella Krahenbuhl, Robert Weber, James Crockett, John Christianson, Eugene Hamilton, Lilia Rodriguez, Thomas Coleman, Francis Lohrenz, and William Larsen have had this four-month experience.

C. *Fellows*: In addition, six men have taken fellowships in the laboratory of one year or longer. These men and their source of support are: Dr. Mario Anache, Rio de Janeiro, Brasil, Agnes Haskell Fellow; Dr. James Crockett, Kansas City, Kansas, Trainee, National Heart Institute; Dr. Fethi Gonlubol, Smyrna, Turkey, Agnes Haskell Fellow; Dr. Sherman Steinzeig, Kansas City, Trainee, National Heart Institute; Dr. Chesterfield Gunn, Bethany, Missouri, Research Fellow, American College of Physicians.

Dr. Chaveng Dechakaisaya, Bangkok, Thailand, fellow sponsored by the Department of Health, Education and Welfare, U. S. Public Health Service, spent three months in the laboratory.

Three men receiving training in enzyme chemistry joined Dr. Grisolia. They are: Dr. Jacob C. Towne, New York City, Trainee, National Heart Institute; Dr. Donald P. Wallach, New York City, Post Doctorate Fellow, National Heart Institute, and Victor R. Rodwell, London, England, U. S. Public Health Funds.

Dr. Sita Ram Kapoor, Ruckonw, India, has been in training with Dr. Kurt Reissmann during 1954-1955. Dr. Kapoor was sponsored by the Rockefeller Foundation.

For the first time the laboratory has offered an elective in cardiovascular diseases to medical students. Doctors L. A. O'Donnell, R. L. Jewell, R. L. Linscheid, M. S. Liggett, G. L. O'Connell, D. E. Raab, H. E. Arst, and Sylvan Busch have been with the unit in this role.

Dr. Chesterfield Gunn, completing a year with the unit, joined Dr. Magoun's laboratory in Los Angeles and is continuing his work in investigating cerebral factors in hypertension. Dr. Mario Anache completed his year, has returned to Rio de Janeiro, and is establishing his own cardio-physiological unit at Hospital dos Servidores.

D. *Visiting Professor*: For the first time the laboratory sponsored a visiting professor in cardiology. The first professor was Dr. Mariano Alimurung, associate professor of medicine, chief of Cardiovascular Section, School of Medicine, Santo Tomas University Hospital, Manila. Dr. Alimurung joined the laboratory for one month, February, 1955. He was a stimulating visitor and bolstered our teaching program at every level.

II. CLINICS, CONSULTATIONS, AND HOSPITAL SERVICE

A. *Clinics*: The laboratory has maintained out patient clinics in general cardiology on Monday and Friday mornings and Wednesday and Friday afternoons. Pediatric heart clinic is held on Wednesday and Saturday morning. A peripheral vascular disease clinic is held on Thursday mornings. Special clinics for research purposes are maintained on Monday afternoon for hypertension and on Tuesday afternoon for angina.

B. *Consultations*: The laboratory also offers consultation service to hospital patients. The total number of consultations and out patients seen by laboratory personnel and Dr. Diehl and Dr. Jordan in the two-year period was 5,764. Of these, 560 were in peripheral vascular disease.

C. *Hospital Service*: During this 24-month period, new bed patient facilities became available with the opening of the chest building. The laboratory maintains an 11-bed service there. The nurse in charge of this area has been Miss Dorothy Thomas. The dietitian has been Miss Dolores Flackmiller, and the social service worker has been Miss Mildred Webb. The residents assigned to the laboratory rotate at two-month intervals through this bed service. Daily teaching ward rounds are maintained by the laboratory. During the resident's second two months on the service, he is assigned to the out patient clinic and has responsibility for the out patient cardiac clinics and the daily interpretation of electrocardiograms.

III. PUBLICATIONS, EXHIBITS, POSTGRADUATE COURSES AND RESEARCH

A. *Publications*: The members of the laboratory published the following papers between May, 1953, and May, 1955:

Dimond, E. Grey; Kittle, C. F., and Lin T. K.: Cardiovascular laboratory, university of Kansas medical center: report of activities of first 24 months, May, 1951-May, 1953, Journal of the Kansas Medical Society 54:509-512 (Nov.) 1953.

Dimond, E. Grey; Santos, E. M., and Lin, T. K.: Occurrence of auricular fibrillation in immediate postoperative period following mitral valvulotomy. Journal of Laboratory and Clinical Medicine 42:799 (Nov.) 1953.

Dimond, E. Grey; Santos, E. M.; Mundy, William, and Calderwood, B. J.: An attempt to establish the presence of a hypocholesterolemic factor in the renal blood of dogs. Journal of Laboratory and Clinical Medicine 42:800 (Nov.) 1953.

Dimond, E. Grey, and Gonlubol, Fethi: Death fol-

lowing angiocardiography, New England Journal of Medicine 249:1029-31 (Dec. 17) 1953.

Dimond, E. Grey, and Berry, F. M.: Transmission of electrocardiographic signals over telephone circuits, American Heart Journal 46:906 (Dec.) 1953.

Dimond, E. Grey, and Jones, T. Reid: Pulmonary artery thrombosis simulating pulmonic valve stenosis with patent foramen ovale, American Heart Journal 47:105 (Jan.) 1954.

Dimond, E. Grey, and Santos, E. M.: Complications following mitral commissurotomy with special reference to auricular fibrillation, Journal of the Kansas Medical Society 55:120 (March) 1954.

Dimond, E. Grey: The general practitioner and the medical school, The Journal of the American Medical Association 156:95, 1954.

Dimond, E. Grey, and Andrews, Martin H.: Clinical thermometers and urinometers, determination of their accuracy, The Journal of the American Medical Association 156:125 (Sept.) 1954.

Dimond, E. Grey: How to conduct a medical program (Hostmanship), GP 11:142 (May) 1955.

Gonlubol, Fethi, and Dimond, E. Grey: Congenital pulmonary arteriovenous fistula, Journal of the Kansas Medical Society 56:146 (Mar.) 1955.

Grisolia, Santiago, and Marshall, Richard O.: Enzymic decomposition of the active intermediate in citrulline synthesis, Biochim. Et. Bioph. 14:446, 1954.

Grisolia, Santiago, and Burris, R. H.: Preparation of glutamate and carbamyl glutamate selectively labeled with deuterium, The Journal of Biological Chemistry 210:109 (Oct.) 1954.

Grisolia, Santiago, and Marshall, Richard O.: Recent advances in citrulline biosynthesis, amino acid metabolism, edited by William D. McElroy and Bentley Glass, The Johns Hopkins Press, Baltimore, 258, 1955.

Grisolia, Santiago; Burris, R. H., and Cohen, P. P.: Fate of deutero-labeled carbamyl glutamate in citrulline biosynthesis, The Journal of Biological Chemistry 210: 761 (Oct.) 1954.

Grisolia, Santiago; Wallach, Donald P., and Grady, Harold J.: Carbamyl transfer with mammalian and bacterial enzymic preparations, Biochim. Et. Bioph. 17:150, 1955.

Grisolia, Santiago; Grady, Harold J., and Wallach, Donald P.: Biosynthetic and structural relationships of compound X and carbamyl phosphate, Biochim. Et. Bioph. 17:277, 1955.

Grisolia, Santiago, and Wallach, Donald P.: Enzymic interconversion of hydrouracil and B-ureidopropionic acid, Biochim. Et. Bioph. 18:449, 1955.

Grisolia, Santiago: The potentiating effect of Digitoxin and Quinidine on dinitrophenol uncoupling of oxidative phosphorylation, Biochim. Et. Bioph. 18:437, 1955.

Grisolia, Santiago: Enzymatic citrulline synthesis methods in enzymology, 2:350, 1955.

Hardin, C. A.; Reissmann, Kurt R., and Dimond, E. Grey: The use of hypothermia in the resection and homologous graft replacement of the thoracic aorta, Annals of Surgery 140:720 (Nov.) 1954.

Hoelscher, B., and Reissmann, K. R.: The combined effects of hypoxia adrenalectomy and thymectomy in parabiotic rats, Endocrinology 54:147, 1954.

Kittle, F.; Reissmann, K. R.; Dimond, E. G., and Schafer, P. W.: Torsion ballistocardiography in cardiovascular surgical patients, J. Thoracic Surg. 27:107, 1954.

Lin, T. K., and Dimond, E. Grey: Reliability of the grading of cardiac murmurs, General Practice 8 (July) 1953.

Reissmann, Kurt R., and Dimond, E. Grey: Torsion ballistocardiography: with special reference to patterns in surgically amenable cardiovascular diseases, Circulation 8:585 (Oct.) 1953.

Reissmann, K. R., and Dimond, E. G.: Is intravenous oxygen therapy possible? Anesthesia and analgesia 32: 426, 1953.

Reissmann, K. R.; Boley, J.; Christianson, J. F., and Delp, M. H.: The serum iron in experimental hepatocellular necrosis, J. Lab. Clinical Med. 43:572, 1954.

Reissmann, K. R.; Coleman, T. J.; Budai, B. S., and Moriarty, L. S.: Acute intestinal iron intoxication, I. Iron absorption, serum iron and autopsy findings, Blood 10:35, 1955.

Reissmann, K. R., and Coleman, T. J.: Acute intestinal iron absorption II. Metabolic respiratory and circulatory effects of absorbed iron salts, Blood 10:46, 1955.

Reissmann, K. R.; Christianson, J.; Boley, T., and Kittle, C.: The relationship of serum iron changes, hepatic function and histological findings in experimental hepatic injuries of various etiologies, Surgery 37:738, 1955.

Reissmann, K. R., and Kapoor, S.: Dynamics of the hypothermic heart muscle (heart-lung preparation), Am. Journ. Physiol., 1955, accepted for publication.

Books: Electrocardiography, by Dimond, E. Grey. Published by the C. V. Mosby Company, 1954.

B. *Exhibits*: Three exhibits were prepared. One, on the autonomic nervous system, was shown to the Kansas City Southwest Clinical Society, at the meeting of the American Academy of General Practice, at the Kansas Medical Society meeting, at the Chicago Medical Society meeting, and at the International Congress of Cardiology. A second exhibit, on the surgical treatment of aortic insufficiency, built in collaboration with Dr. Frederick Kittle, won first prize at the Kansas City Southwest Clinical Society meeting. A third exhibit, on pulmonary stenosis, won first prize at the Kansas Medical Society meeting.

C. *Research*: Clinical investigation, especially in the field of hypertension and angina, has been carried on. Laboratory work has been in the area of iron metabolism and hypothermia (Dr. Reissmann), effect of trace metals in cholesterol metabolism (Dr. Curran), effect of heparin on adenosine triphosphate (Dr. Dimond), and basic enzyme systems of the heart (Dr. Grisolia).

D. *Postgraduate Courses*: The laboratory has had considerable responsibility for postgraduate medicine.

In 1954 two courses were organized and presented. The first was jointly sponsored by the Kansas Heart Association and the Kansas City, Missouri, Heart Association and was a one-day program.

The second 1954 program was a four-day course restricted to auscultation and physical diagnosis. The guest speakers were Dr. Gordan S. Myers and Dr. Edward Wheeler, Boston, Dr. J. Willis Hurst, Atlanta, and Dr. Ernest Craige, Chapel Hill, North Carolina.

In 1955 two more programs were organized and presented. A two-day program on recent advances in heart disease, again sponsored by the Kansas Heart Association and the Kansas City, Missouri, Heart Association, was presented in February. The guest speakers were Dr. Louis Katz, Dr. Henry Russek, and Herman Hellerstein. In March a four-day program in electrocardiography was presented.

In addition, two correspondence courses in electrocardiography are maintained by the laboratory. In this two-year period, 277 physicians enrolled in these correspondence courses.

IV. DIAGNOSTIC PROCEDURES

A. *Electrocardiograms*: During this two-year period 14,569 electrocardiograms were recorded, mounted, and interpreted. In the previous two-year period (1951-1953), 13,546 had been done. The records have been 12-lead tracings, obtained on direct writing equipment. A photostatic copy of each record is placed on the chart; the original is filed in the cardiovascular laboratory. Each record is cross indexed, according to name and according to diagnosis. The technician responsible for this area has been Miss Margaret Delich, assisted by Inez Claxton, Ilah Plumb, Mary Baker, and Bernice Bain.

B. *Peripheral Vascular Studies*: A weekly clinic in peripheral vascular disease has been maintained. The responsible staff man has been Dr. Robert Jordon. The residents in medicine and the fellows in cardiology rotate through this clinic. Five hundred and sixty patients were seen in this clinic. In addition to the medical staff, an attending chiropodist is present, Dr. Irvine Waxman. Detailed peripheral work-ups were done on about one-fifth of these patients:

Plethysmograms	64
Skin Temperatures	76
Landis Test	44
Oscillometric Study	42
Cold Pressure Study	5
Posterior Tibial Block	27
Lumbar Block	35
Stellate Block	5
Intra-arterial Priscoline	17

The technician responsible for this work is Mrs. Lavina Goering.

C. *Cardiac Catheterization*: Cardiac catheterization has continued to be a heavy responsibility of the unit. Dr. T. K. Lin has been responsible for this area. Dr. Mario Anache and Dr. Fethi Gonlubol have assisted him and have been trained in the technique. The technicians have been Herbertine Clark, Barbara Cullen, and Donna Sims. In this two-year period, 244 patients were catheterized. (In the previous two-year period, 130 had been done). The first death since the formation of the team occurred. This patient was two months old. As the catheter entered the right ventricle, ventricular fibrillation occurred. Cardiac massage was immediately begun and continued for two hours. Autopsy revealed atrioventricular communis and fibroelastosis of the auricle.

The principal temporary complications were: chilling, 5; nausea, 3; vomiting, 1; fever, 2; venous spasm (severe), 1; bundle branch block (temporary), 1; complete A-V block (temporary), 1; ventricular tachycardia (temporary), 9.

D. *Angiocardiography*: Fifty-three angiocardiograms were done. These were done by Dr. T. K. Lin and Dr. Antonio Diehl with radiographic help from Dr. Galen Tice, Dr. Donald Gerrmann, and Dr. Karl Youngstrom of the Department of Radiology. One death occurred in a three-week old male, immediately after the injection of the contrast agent; transposition of the great vessels was present.

E. *Aortograms*: Twenty-six translumbar aortograms were done by the laboratory. These were done by Dr. T. K. Lin. No deaths occurred. Extravasation of dye along the aorta occurred in two without complications.

F. *Ballistocardiograms*: The shin-bar apparatus was used and 280 ballistocardiograms were recorded on 251 patients.

G. *Phonocardiograms:* These (120) were done by Dr. Sherman Steinzeig, Dr. Fethi Gonlubol, and Dr. Mario Anache. This procedure is very exacting and time consuming.

V. SURGICAL PROCEDURES

The members of the laboratory, working in association with the Department of Surgery and the Department of Pediatrics, had the opportunity of following a considerable number of cardiovascular surgical procedures. The surgery was done by Dr. Frank Allbritten, Dr. Creighton Hardin, and Dr. Frederick Kittle.

A. *Patent Ductus Ligation.* Twenty-four ligations were done; 16 were also transected.

B. *Coarctation of the Aorta.* Eight resections were done, with a graft necessary in one.

C. *Blalock Procedure* (Subclavian artery anastomosed to pulmonary artery). Thirteen attempts were made. These patients were frequently small infants in extremis and for whom surgery was a calculated gamble.

D. *Brock Procedure* (Pulmonary valvulotomy). Twenty-two valvulotomies were done.

E. *Pott's Procedure* (Aortic pulmonary artery anastomosis).

F. *Mitral Valvulotomy.* Seventy-five valvulotomies were done.

G. *Tricuspid Valvulotomy.* One.

H. *Aortic Plastic Valve* (Hufnagel). Six plastic valves have been inserted.

I. *Aortic Valvulotomy.* Five.

J. *Pericardectomies for Constrictive Pericarditis.* Two patients were operated upon with good results.

K. *Talc Installation in Pericardium.* Two.

L. *Aneurysm Repair.* This work has been done by Dr. Creighton Hardin: abdominal aneurysm, 22; thoracic aneurysm, 3; femoral aneurysm, 5; popliteal aneurysm, 2; carotid aneurysm, 5; repair of Leriche syndrome, 17.

M. *Thoraco-Lumbar Sympathectomy,* 11. Six patients, five bilateral.

N. *Exploratory Cardiotomies,* 11.

The majority of these patients had rheumatic valvular disease and cardiotomy was done because the possibility of mitral stenosis was suspected but atypical clinical findings were present.

O. *Inferior Vena Cava Ligation,* 2.

P. *Excision Pericardial Cyst,* 1.

Q. *Auricular Septal Defect Repair,* 2.

VI. GRANTS

The medical school state budget funds continue to be the basic major support. The National Heart Institute, through its Undergraduate Cardiovascular Teaching Grants, has continued to be the principal outside support. This yearly grant has permitted us to add personnel, obtain equipment, and develop the laboratory in a manner which would otherwise be impossible.

The National Heart Institute has also supported, as trainees, Dr. James Crockett, Dr. Sherman Steinzeig, Dr. Jacob Towne, Dr. Donald P. Wallach, and Victor Rodwell.

Income from the Agnes Haskell Endowment has been utilized for the support of the first Haskell fellow, Dr. Fethi Gonlubol.

The McIlvaine Trust awarded the laboratory sufficient funds to permit the equipping of a four-room laboratory suite and also partial support of the director of this unit. This laboratory, designated the Frederick McIlvaine Trust, is a gift of Lettie B. McIlvaine in memory of her husband. Research in the field of enzyme metabolism, as it relates to heart muscle, is carried out here on the direction of Dr. Santiago Grisolia.

The McIlvaine Trust also made a substantial grant to Dr. George Curran's work in the field of cholesterol metabolism.

A grant from the National Heart Institute, made to Dr. Reissmann and Dr. Tom Hamilton, Department of Microbiology, for investigation of pulmonary hypertension, was received in 1954 and 1955.

The American Heart Association has made a major contribution in the support of Dr. Curran and Dr. Santiago Grisolia as established investigators.

The Kansas Heart Association helped in the maintenance of the cardiac catheterization team in 1954.

Other support came from the Peggy Nygaard Fund and the Jules Friburg Memorial Fund.

SUMMARY

The second two years of operation of the University of Kansas Cardiovascular Laboratory ended May, 1955. The staff now consists of two clinical cardiologists and three basic investigators. One more man will be added this year to develop the peripheral vascular section.

In the first four years since the opening of the laboratory, 28,115 electrocardiograms have been taken, 9,530 consultations given, 374 cardiac catheterizations done, 79 angiograms made, and approximately 361 major cardiovascular operations performed at the University of Kansas Medical Center. The Cardiovascular Laboratory, the Department of Surgery, and the Department of Pediatrics have participated jointly in this work.

SUMMARY OF CARDIOVASCULAR ACTIVITIES, KUMC, 1951-1955

	1951-1953	*1953-1955*
Consultations	3,766	5,764
Electrocardiograms	13,546	14,569
Cardiac Catheterizations	130	244
Angiocardiograms	26	53
Operations	130	231

No one treatment is successful with every alcoholic patient. The needs of alcoholics vary both in the psychic and physiological realms. It is recognized that a "total push" is the best and most successful method of bringing the largest number of alcoholics to recovery. One physician may minister to the physical needs of the patient; another may lead him to an integrated emotional life through psychotherapy.

PRESIDENT'S PAGE

DEAR DOCTOR:

Have you had your vacation? To those of you who have, welcome back. To those of you who have not, bon voyage.

You should have a vacation. It seems to me that each doctor should make it a must. The working day is so long mental fatigue comes easily, and a chip on the shoulder looms larger and is more quickly toppled over. You owe it to yourself and your patients since you will return in a much better and clearer frame of mind.

September has arrived and all committees will be meeting in the next few months. Some have already done so, and it is hoped that all members will be attentive and forthgiving with advice and wisdom. These committees are the backbone of this organization. Their effectiveness depends upon your contributions.

Fraternally,

Clyde H Miller M.D.

President

EDITORIAL COMMENT

What's Wrong with Medical Organizations?

Editor's Note. The following report, prepared by the American Medical Association, gives a partial answer to the question above.

A nationwide survey of physicians, commissioned by the AMA, shows that medical organizations can profit by internal inspections. Difficulties may be minor, but, according to some physicians, medical organizations aren't hitting on all cylinders.

Medical organizations must give increased attention to the problem of boosting meeting attendance and devote more efforts to drawing all members into active society participation. Individual physicians need more information about actual benefits of membership as well as about policies and projects of their medical organizations. Too many physicians apparently don't know the facts about their own organizations.

Survey findings brought the need for attention to some of these problems into sharper focus. For example, only half of the physicians in this country report they are active in county and state organizations. One doctor in four says he didn't vote in his local society's last election. More than a third say they belong only to medical specialty groups not associated with the AMA, or that they are more active in these other organizations.

Furthermore, about half of the doctors think of county and state societies as being different from the AMA, when in reality these organizations compose the national association. Additional break-downs in the lines of communications between individual members and their organizations show up in misunderstandings about medical policies and lack of knowledge about organizational activities and services. A typical misconception has to do with dues; only half of AMA members actually know what national dues are, and most doctors overestimate rather than underestimate dues.

It's encouraging to find that 90 per cent of doctors in private practice report they are members of the AMA. More than half of the AMA members surveyed reported they belong to the association because it's customary, it's the doctors' organization, or they believe in its policies. Yet 15 per cent say membership is necessary for hospital affiliation or that it's compulsory. Informed physicians know that hospitals, not medical societies, determine rules and regulations for securing hospital privileges. And, no physician is forced to associate himself with any medical organizations; if he joins, he does so voluntarily.

Many doctors cite AMA services or activities which they like, such as the JOURNAL, meetings and conventions, information and exchange of ideas, and legislative action. But others say the association is not representative, criticize it for being remote and uninterested in the individual physician, and complain about its conservatism. Consequently, about a fifth of the members say they do not get value received for their AMA dues.

Although survey questions asked only about physicians' opinions in regard to AMA services, activities, and policies, similar criticism would no doubt have been given had doctors been asked their opinion about their state associations. All along the organizational line, it's apparent that a better informational job needs to be done. The aid of state and county groups is needed to help sell physicians on the merits of cooperative action through medical organizations. For when a physician criticizes AMA, he is actually criticizing his local society and his state association, too. When his society joins in the complaining, the breech within the ranks widens.

In the minds of some medical men a mythical "giant" has been built up in AMA. Newspapers have contributed to this illusory creation. AMA *is* an influential organization, and since it comprises the greatest percentage of physicians in this country, it rightly claims title of official spokesman for the profession. Yet over the years critics of organized medicine have chiseled a psychological rift by saying, "You individual MDs are ok and you're doing a good job—but AMA off in Chicago or Washington is the villain!" In reality, the individual physician is AMA. Repetition of this idea has made it harder—or less desirable—for an individual physician to identify himself with the AMA.

This insidious dissociation process may be a contributing factor to the splintering off into smaller specialty groups which has been becoming more widespread in the past few years. Unaffiliated organizations are less controversial; with one or two exceptions they have received far less attention in the public press. When physicians who said they were more active in these specialty groups were asked why, they gave these replies: my specialty; local, closer; more interesting; smaller, more social; more worthwhile; easier to get to meetings. One clue for alert societies aiming at greater member participation was given in the response by some doctors that "there's nothing to do in the AMA."

Although the scientific programs of specialty groups will always hold appeal for numbers of physicians, the danger lies in the tendency of such organizations to begin speaking out separately on

non-scientific matters affecting medicine. When many organizations begin professing to speak for medicine, the public becomes confused and the over-all impression is given that the members of the medical profession can't agree among themselves. Nobody denies the right of members to criticize their own organizations or to disagree with their actions; yet there are times when it is vital for medicine to present a united front. Those who believe in democracy accept the premise that the opinions of the majority should prevail—until the minority can change the opinions of that majority.

The links in the chain of medical organization are the county and state associations. When poor attendance weakens their effectiveness, the collective strength of the entire profession is diminished. According to the survey, 50 per cent of the doctors attend most meetings of their local or county society. Yet 6 per cent say they attend no meetings, 16 per cent very few, 9 per cent some, and 9 per cent half. The problem of meeting attendance appears to be greatest in the East, where only 38 per cent of the doctors say they attend most meetings. Western states evidently chalk up the greatest attendance since 61 per cent of the doctors say they turn out for meetings. Central and Southern states fall midway between, with 54 per cent in the Midwest and 56 per cent in the South attending most meetings. One or two other interesting sidelights were revealed in the study. For example, internists least often say they attend county meetings. Only 35 per cent of the internists say they attend most meetings as contrasted with an average of 50 per cent of all other types of doctors. Internists also least often say they voted in the society's last election of officers.

Doctors in the East least often believe they get their money's worth in return for dues (32 per cent as against an average of 23 per cent.) Here again internists reflect a less favorable attitude toward medical organizations than other doctors. Twenty-six per cent of the internists feel full value is not received in return for dues, while general practitioners least often express dissatisfaction on this count (21 per cent).

Another revealing discovery is that doctors rate the American Dental Association higher in terms of favorable impressions than they do their own medical organizations. About three out of four doctors say their impressions of both the AMA and the ADA are all good or more good than bad. Yet, one doctor in 12 says he has negative impressions of AMA while only one in 50 is critical of the dental association. Doctors rank the American Bar Association in third place.

Time after time in the study the individual physician proved to be far more critical of his colleagues and of medical organizations than the public. For example, 24 per cent of the doctors say the public looks upon AMA as a doctors' union and medical trust. Yet, this survey shows only 37 per cent of the public has this opinion. During the past few years, the medical profession has worked hard to regain the confidence and good will of the public. Now it's obvious that some concentrated internal public relations efforts are necessary in order to rekindle physicians' enthusiasm and interest in medical organizations. Larger numbers of physicians ought to be pulling their own weight in their societies, rather than dragging their heels and allowing a few men to serve as standard bearers. Medical organizations must concentrate on doing a better job of informing their members about their activities, policies, and services.

Physicians, in an effort to revamp their service programs for the public and to stave off a government medical program, have taken it on the chin from many critics. Most have accepted just criticisms humbly and moved ahead to correct sources of dissatisfaction. Perhaps it's time now to stop being on the defensive—to help physicians regain a sense of pride in the medical organizations to which they belong. An organization whose aims are "to promote the science and art of medicine and the betterment of public health" need not apologize for its efforts to advance these noble objectives.

The Chaplain and Medicine

The chaplain in the hospital has an assignment that is unique: to be clerical and (help be) medical. He has access to the critically ill list, emergency room calls, the surgical department—in fact, he is today to be found anywhere in the hospital on call for his particular services to patients or to their visiting relatives and friends. His assignment is to help people of all races, colors, and creeds, regardless of his particular religious denomination. In this way the doctor is most often helped to shoulder the burden brought to him in the care of the seriously ill.

Friendliness is one of the virtues of the chaplain. Frequently there are gravely ill patients who have no relatives or friends to be contacted. These patients are lonely and depressed mentally, conditions that do not help recovery. A friendly hospital visit by the chaplain and his help in reaching acquaintances do much to give the patient a "lift" and may speed his getting well.

The role of the chaplain as a minister would seem to be his "mission" in his relationship to the patient and the doctor. Here, as the minister, he attempts to soothe the patient by showing him that regaining his spiritual strength will help in the recovery of his

physical strength. He may even resort to the dogma "There was never an atheist in a foxhole," knowing full well that patients become pensive while ill and take inventory of themselves. Even though they never professed religious inclinations, they may feel they should go along with the idea since "There might be a lot to gain and nothing to lose."

Then, of course, there is the facetious side to the chaplain's talk to the seriously ill (who will not take to the idea of religion): the talk will sometimes take the patient's mind off his ailment and thus give him physical relief.

The chaplain acts further as a liaison officer between the patient and the doctor (and the family). On many occasions the doctor asks the chaplain to talk to the family or friends, or even the patient, on various pertinent subjects regarding the illness. Quite often the procedure is reversed, and the patient or the chaplain confers with the doctor.

The question arises as to how a chaplain should approach a patient. There are many methods, depending on the kind of patient and the kind of illness. If the patient is surgical, a chat with the relatives during and immediately after the operation would be in order. Making an appearance to say a cheerful "hello" to the patient for the first two or three days is probably all right. However, it would be wise to wait about three days before making a visitation, barring an emergency, because of the following: the patient may become frightened or worried at the presence of the chaplain, or he may not be receptive to the chaplain's presence because of fatigue, sleepiness, or too many visitors in the room, or he may even go so far as to think the chaplain is a meddler. On the other hand, if the patient is a medical case, this condition has existed for at least a short while prior to hospitalization and the call can be made promptly.

The visit should be brief in most cases. There will be times, however, when the patient will probably ask that the chaplain remain and chat with him; should this occur, moderacy should be the rule. Very little concerning the patient's illness should be said; rather, the talk should be about more pleasant ideas, such as nice things about the patient's relatives, etc. Occasional flattery of these individuals does no harm. I have seen persons with cancerous conditions completely forget about their ailments as their eyes light up with pleasant reminiscences during such talks.

Most important of the "don'ts" for chaplains is: do not offer medical advice to the patient or attempt to pass judgment on the medical care being given him by his doctors, nurses, and other hospital personnel. Should he see the conversation drifting in this direction, he should immediately steer clear and switch to other topics, always being sure, however, to avoid argumentative subjects, as politics, stock market, etc.

The doctor feels more secure if the chaplain supports him should the condition of the patient worsen. Also, the doctor is appreciative if the chaplain come to his defense should certain wild, unfounded malicious rumors and accusations be thrown at him by well-meaning (?) but emotionally upset relatives in the case of unfavorable progress of the patient.

Close cooperation of the chaplain with the doctor on the case is a necessity. The chaplain is seen to be the "man-between" in the making of contacts of distantly located relatives and friends; he is the man to help raise the mood and spiritual level of the patient in order to create a better attitude which is conducive to greater and faster recovery.

It must be reiterated that he is the friend of the doctor.—*William W. Abrams, M.D., Kansas City.*

Society Studies Indigent Care Program

The Riley County Medical Society is currently studying statistics to determine the percentage of payment to physicians for caring for indigent patients under the present program of the Department of Social Welfare. The society is dissatisfied with the allowance of $2.00 per family per month, feeling that the amount is inadequate and unrealistic for covering medical and surgical fees for office and house calls and hospital care.

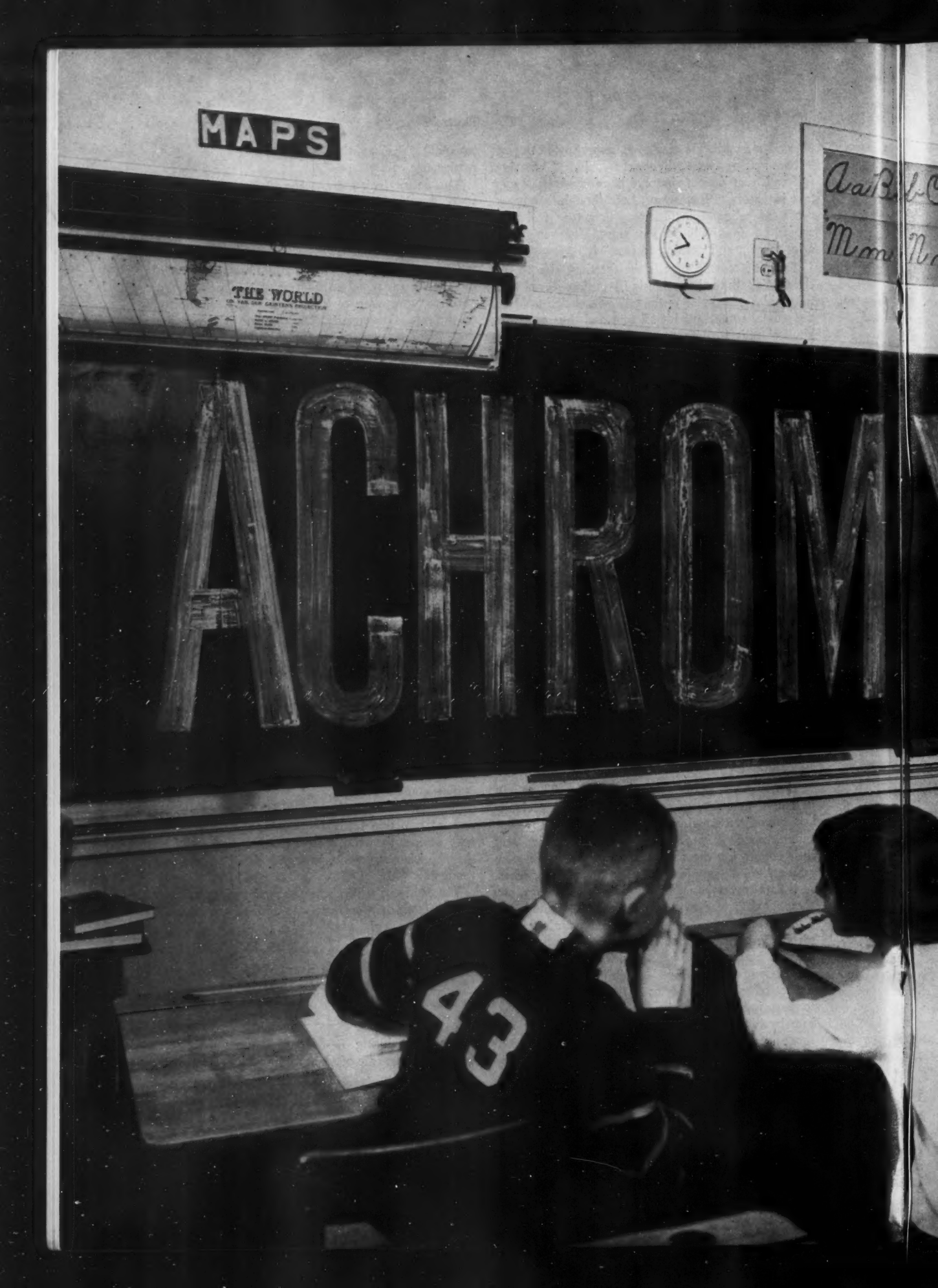
The society has set up a minimal fee schedule for indigent care based on the minimal Blue Shield schedule for medical and surgical fees for hospitalized patients and a comparable schedule for office and home care. Allowances are also made for laboratory and x-ray procedures in the office. Physicians render statements monthly to their society's Committee for Indigent Care.

The committee scrutinizes all statements and issues checks to individual physicians, pro rating the amount available from the $2.00 per family allowance against the total charges. The sum received by the physician represents payment in full for services rendered.

The study so far indicates that physicians are collecting from one-fourth to one-third of the amounts billed each month.

At the close of the first quarter of 1956, according to the Treasury Department, one person of every four in the nation owned one or more savings bonds.

Hospitals during 1955 received more than $885 million for the care of eight million Blue Cross members.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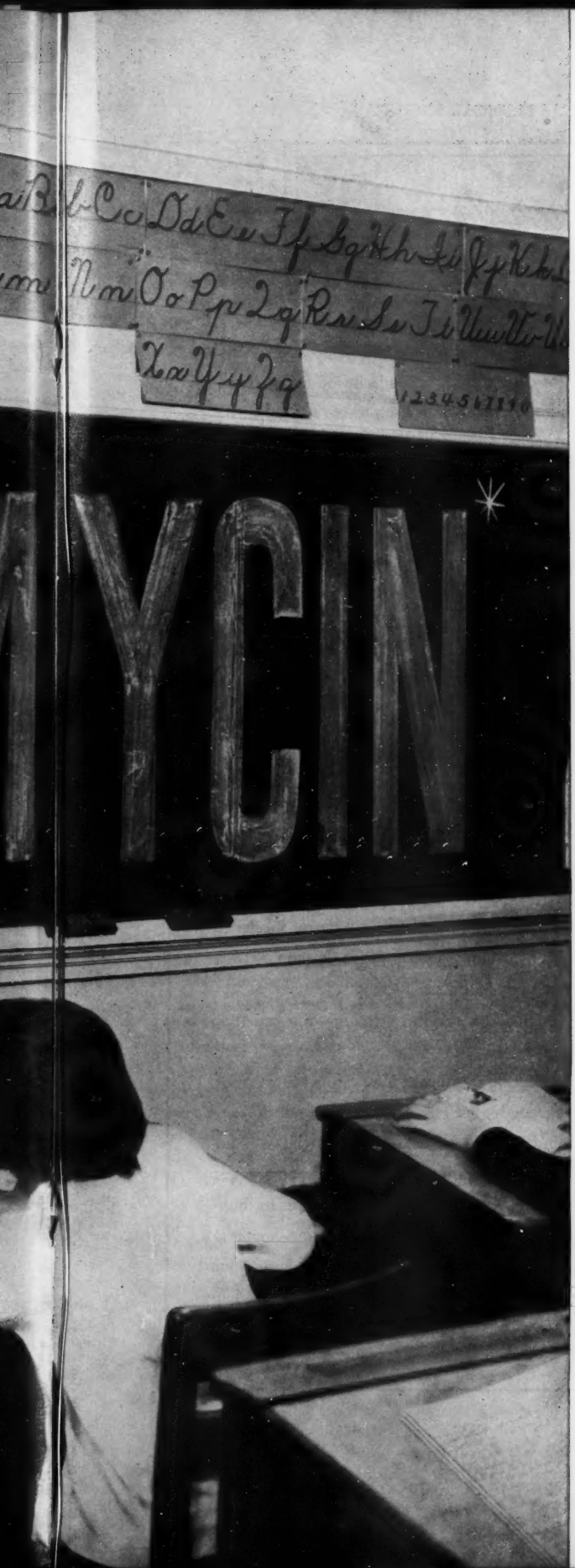

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January and his associates[1] have written on the use of tetracycline (ACHROMYCIN) to treat 118 patients having various infections, most of them respiratory, including acute pharyngitis and tonsillitis, otitis media, sinusitis, acute and chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial pneumonia, and lobar pneumonia. Response was judged good or satisfactory in more than 84% of the total cases.

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ACHROMYCIN with STRESS FORMULA VITAMINS. Attacks the infection—defends the patient—hastens normal recovery. For severe or prolonged illness. Stress formula as suggested by the National Research Council. Offered in Capsules of 250 mg. and in an Oral Suspension, 125 mg. per 5 cc. teaspoonful.

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[1]January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

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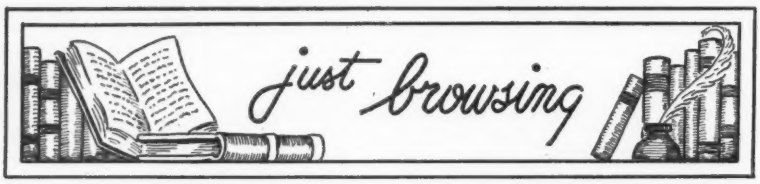

Publication of Alan Beck's description of a girl in the August issue of the JOURNAL *demands printing also his classic, "What Is a Boy," which follows.—O. R. C.*

Between the innocence of babyhood and the dignity of manhood we find a delightful creature called a boy. Boys come in assorted sizes, weights and colors, but all boys have the same creed: To enjoy every second of every minute of every hour of every day and to protest with noise (their only weapon) when their last minute is finished and the adult males pack them off to bed at night.

Boys are found everywhere—on top of, underneath, inside of, climbing on, swinging from, running around or jumping to. Mothers love them, little girls hate them, older sisters and brothers tolerate them, adults ignore them, and Heaven protects them. A boy is Truth with dirt on its face, Beauty with a cut on its finger, Wisdom with bubble gum in its hair, and the Hope of the future with a frog in its pocket.

When you are busy, a boy is an inconsiderate, bothersome, intruding jangle of noise. When you want him to make a good impression, his brain turns to jelly or else he becomes a savage, sadistic, jungle creature bent on destroying the world and himself with it.

A boy is a composite—he has the appetite of a horse, the digestion of a sword swallower, the energy of a pocket-sized atomic bomb, the curiosity of a cat, the lungs of a dictator, the imagination of a Paul Bunyan, the shyness of a violet, the audacity of a steel trap, the enthusiasm of a firecracker, and when he makes something he has five thumbs on each hand.

He likes ice cream, knives, saws, Christmas, comic books, the boy across the street, woods, water (in its natural habitat), large animals, Dad, trains, Saturday mornings and fire engines. He is not much for Sunday School, company, schools, books without pictures, music lessons, neckties, barbers, girls, overcoats, adults or bedtime.

Nobody else is so early to rise, or so late to supper. Nobody else gets so much fun out of trees, dogs and breezes. Nobody else can cram into one pocket a rusty knife, a half-eaten apple, three feet of string, an empty Bull Durham sack, two gumdrops, six cents, a slingshot, a chunk of unknown substance and a genuine super-sonic code ring with a secret compartment.

A boy is a magical creature—you can lock him out of your workshop, but you can't lock him out of your heart. You can get him out of your study, but you can't get him out of your mind. Might as well give up—he is your captor, your jailer, your boss and your master—a freckle-faced, pint-sized, cat-chasing bundle of noise. But when you come home at night with only the shattered pieces of your hopes and dreams, he can mend them like new with the two magic words—"Hi, Dad!"

THE MONTH IN WASHINGTON

Editor's Note. The following summary of Washington news was prepared by the Washington office of the A.M.A. for distribution to state and regional medical journals.

In terms of actual health bills passed and sums of money appropriated, the 84th Congress which ended just a few weeks in advance of party presidential conventions undoubtedly set some records. Measures ranged from the far-reaching program of disability cash payments to a bill for the commissioning of male nurses in the armed services.

In between are a wide variety of measures which, in the opinion of Secretary Folsom, secretary of Health, Education, and Welfare, gives "promise of immediate and substantial progress on a wide front in the improvement of the nation's health."

Both Mr. Folsom and the President deplored the fact that Congress had not acted on their plan for federal aid to medical schools, but Congress decided this was one of the subjects that needed more study before taking any further action. In addition Mr. Folsom expressed disappointment that nothing had been done on authority for pooling arrangements among small health insurance companies and the long-dormant plan for a health reinsurance fund.

On medical research funds, the administration this session asked for the largest amount of money ever requested in one year. The appropriation finally voted was even larger, some $170 million. On top of this, Congress in its final hours appropriated nearly $80 million to carry out new legislation just passed.

Here are the highlights of major health bills approved by the 84th Congress:

Social Security Amendments—Changes in the 21-year-old social security law now include: (1) Old Age and Survivors Insurance payments to disabled workers at age 50, paid from a "separate" fund, (2) extension of social security to some 250,000 dentists, lawyers, osteopaths, and other self-employed persons, (3) lowering of retirement age for social security purposes for women from 65 to 62, (4) earmarked payments for medical care of public assistance recipients, and (5) increase of payroll deductions by one-half of 1 per cent and three-eighths of 1 per cent for the self-employed.

Laboratory Research Facilities—The Hill-Bridges bill for $90 million in construction grants over three years to public and non-profit institutions to erect research facilities started out in the Senate as a bill to aid research in crippling and killing diseases but wound up for research in all "sciences related to health."

Health Amendments Act—The so-called little omnibus health bill provides for federal grants for training of public health specialists, professional nurses qualified for teaching and administrative jobs, and for practical nurses—plus a two-year extension beyond next July 1 of the 10-year-old Hill-Burton hospital program, and special projects grants for mental health studies and demonstrations.

Medical Care for Military Dependents—A long-sought goal of the Defense Department was enactment of a permanent program of medical care for dependents of armed services personnel either in military hospitals and clinics or through private sources. It is scheduled to begin early in December.

National Library of Medicine—Another proposal long in the making was the reestablishment of the Armed Forces Medical Library as the National Library of Medicine. For administrative purposes, Congress put it under the Department of HEW, but left up to the 17-man board of regents the selection of site—in all likelihood in the Washington area.

Sickness Survey—Special and continuing surveys on the extent of illness and disability in the U. S., along with medical care being offered, have been authorized—the first detailed study of it kind in over 20 years. The work will be done by the Public Health Service.

Water Pollution Control—The PHS is authorized to make grants to states and communities to help in construction of sewage disposal plants, at the rate of $50 million a year for 10 years.

Some other measures signed into law by the President were: establishment of a mental health program for Alaska, budget increases for additional staff for the Food and Drug Administration along with a new headquarters building for modern laboratories, provision of medical care for employees and dependents of the State Department abroad in U. S. military facilities, a $400,000 fund to finance the holding of the World Health Assembly in this country in 1958 (which is the 10th anniversary of the founding of the World Health Organization), and the commissioning in the armed services of osteopaths.

The new surgeon general of the PHS is Dr. Leroy E. Burney, a career officer in the commissioned corps and for 10 years commissioner of health for the state of Indiana. Until his nomination by the President he was deputy chief of the PHS Bureau of State Services. Dr. Burney received his medical degree from Indiana University.

The federal government withdrew from the allocation of the Salk poliomyelitis vaccine just 15 months after the first release of the vaccine, but federal grants to states to help finance inoculation programs continue.

Clinicopathological Conference

Recurrent Pulmonary Infiltration, Eosinophilia, and Terminal Neurologic Signs

CASE PRESENTATION

The case for consideration today is that of a 44-year old white woman who was first admitted to this hospital on January 23, 1949, and who expired here on January 29, 1955, during her sixth admission.

On her first admission she complained of a productive cough of two and one-half years duration. She had previously been in good health with the exception of recurrent upper respiratory symptoms which she attributed to hay fever and sinusitis. The cough was present in some degree at all times, but it was most severe and most productive in the morning and at night. The sputum was described as being greenish-yellow and of a stringy consistency. She estimated that she expectorated about one-half cup of sputum each day.

During the two years preceding her admission she had had recurrent bouts of fever which were attributed to respiratory infections, and she had had a gradual loss of strength and a 20-pound weight loss. Numerous skin tests had been performed, and she was placed on an elimination diet because she was allergic to many foods. She continued to be ill and required frequent parenteral medication for the relief of paroxysms of coughing and dyspnea.

Six months before admission she had had severe pneumonia, associated with occasional blood-tinged sputum, which improved only slowly on treatment with penicillin and sulfadiazine. Two months prior to admission she suffered a relapse and was hospitalized elsewhere, but she did not do well and was transferred to this hospital for evaluation.

Both of the patient's parents were living and well. One brother died at the age of six months; we do not know the cause of his death. The patient had two living sisters, one of whom had occasional urticaria. Her husband was living and well. They had no children.

In 1928 she had a tonsillectomy, and in 1933 a submucous resection was done. An appendectomy was performed in 1940, and an ovarian cyst was also removed at that time.

She was a native of the midwest and had lived here all of her life with the exception of a few months residence in California in 1945. She did not use alcohol or tobacco and took no home remedies for her symptoms. She had occasional mild frontal headaches. There was progressive exertional dyspnea and some degree of orthopnea, but no ankle edema had been experienced. She had not had nocturia, frequency, or hematuria, and did not complain of gastrointestinal symptoms. The menstrual history was normal.

The patient's first admission to this hospital was January 23, 1949, to March 12, 1949, at which time it was noted that she was somewhat emaciated and appeared to be chronically ill. She was in acute respiratory distress. The blood pressure was 100/60, and the pulse was 120 and rhythmical. The head and neck were normal except that the nasal mucosa was injected, and there was a profuse serous discharge. She had a slight kyphosis, and coarse and fine moist rales were heard over both lung fields. The breath sounds were decreased over the left chest. The heart was normal in size, the tones were good, and no murmurs were heard. There was thought to be minimal clubbing of the fingers.

The urinalysis on this admission was normal, and the red cell count was 4,500,000. The white count was 20,000 on admission with 57 per cent neutrophils, 18 per cent lymphocytes, 17 per cent eosinophiles, and 7 per cent monocytes. Serologic tests for syphilis were non-reactive. The non-protein nitrogen was 30 mg. per cent, the creatinine was 1.2 mg. per cent, the blood sugar was 80 mg. per cent, and the carbon dioxide was 62 volumes per cent. The sedimentation rate was 19 mm. in one hour. Skin tests for tuberculin, blastomycin, and coccidioidin were negative, but the histoplasmin test was positive. The complement fixation test for histoplasmosis was negative. The sputum was cultured on several occasions, but it was never found to contain acid-fast bacilli.

The patient was treated with potassium iodide, aminophyllin, penicillin, khellin, and postural drainage. She had a low grade fever during the first few days of her hospitalization but then became afebrile. She was considerably improved at the time of her discharge.

At her second admission (May 12, 1949, to May 15, 1949) she was found to have gained 14 pounds and had no symptoms except that she tired easily.

On April 23, 1950, the patient was admitted for the third time in order that her condition might be

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Edited by Jesse D. Rising, M.D., and Mahlon Delp, M.D., from recordings of the conference participated in by the departments of medicine, pediatrics, surgery, radiology, and pathology of the University of Kansas Medical Center as well as by the third and fourth year classes of medical students.

evaluated further, and she was dismissed on April 28, 1950. She had had occasional upper respiratory infections and a productive cough, but she had gained 22 pounds and seemed to feel well. Sputum cultures and guinea pig inoculations were again negative for acid-fast bacilli. The radiologist described a "shifting type of pneumonitis."

She was admitted a fourth time, October 21, 1952, to November 7, 1952, because of increasing symptoms and productive cough. She complained of shortness of breath and weight loss in spite of treatment at home with antibiotics, antihistaminics, and postural drainage. The physical examination at this time was essentially the same as it was on her first admission.

The urinalysis was within normal limits. The red count was 4,250,000 with 12.6 gm. of hemoglobin, and the white count was 13,150 with 65 per cent neutrophiles, 13 per cent lymphocytes, 19 per cent eosinophiles, and 3 per cent monocytes. Skin tests were repeated and found to be negative except for an equivocal histoplasmin reaction. Oxygen and carbon dioxide studies on arterial blood revealed an oxygen capacity of 15.6 volumes per cent and carbon dioxide capacity of 44.5 volumes per cent before exercise; an oxygen capacity of 13.9 per cent with a carbon dioxide capacity of 43.8 per cent during exercise; and an oxygen capacity of 15.4 volumes per cent and a carbon dioxide capacity of 45.1 volumes per cent after exercise. Bacteriologic examination of the sputum again failed to reveal acid-fast bacilli, but Histoplasma capsulatum was reported in some of the sputum cultures. A pneumococcus was also found on routine sputum cultures. The complement fixation test for histoplasmosis was positive at this time.

Her treatment was continued as before with the addition of corticotropin and cortisone. She improved satisfactorily and was discharged on cortisone, antibiotics, and bronchodilators. Her vital capacity at the time of discharge was 1700 cc.

On August 2, 1953, the patient was readmitted for evaluation and was dismissed on August 6, 1953. Sputum cultures were negative for Histoplasma capsulatum, but the patient had a positive skin test and complement fixation test for histoplasmosis. She was discharged without any change in therapeutic regimen. After her dismissal she continued to do well and had no symptoms referable to her respiratory system, but in October, 1954, she began to complain of numbness and paresthesias of the left side of the face. She was seen by her family physician who told her that she had Bell's palsy. She was subsequently seen here as an outpatient, but no facial paralysis or weakness was noted.

Two months prior to her last admission the patient was in an automobile accident and received a blow to the right maxillary and frontal area. Following this she complained of frequent mild headaches, and it was thought that there was some change in her personality. On January 11, 1955, she developed a severe frontal and right temporal headache and had an episode of vomiting. One week after this (and two days before her sixth admission to this hospital), her speech became slow and slurred, and she became lethargic. She was hospitalized elsewhere, but because of increasing lethargy and right hemiparesis, she was transferred to this hospital.

The patient's final admission to the University of Kansas Medical Center was on January 20, 1955, at which time she was in a good state of nutrition but was extremely lethargic. She was well oriented and cooperative when kept awake. Her temperature was 99.6 degrees, and her respiratory rate was 28 per minute. The pulse rate was 68, and the blood pressure was 120/65. No abnormalities were noted in the skin. Her speech was slurred. Ocular movements were normal, but the pupils were dilated and reacted only slightly to light. There was definite papilledema on the right and a suggestion of it on the left. Her tongue did not deviate on protrusion. Her neck was stiff. There was a right hemiparesis with Babinski's sign on the right. A few coarse rales were heard in both lung fields, but there were no expiratory wheezes. She did not seem to be in respiratory distress. The remainder of the physical examination was negative.

The red cell count was 4,400,000 with 12.4 gm. per cent of hemoglobin. The white count was 9,500 with 65 per cent neutrophils, 9 per cent eosinophils, 24 per cent lymphocytes, and 2 per cent monocytes. The urinalysis did not reveal any abnormalities. The blood non-protein nitrogen was 42 mg. per cent, creatinine was 1.5 mg. per cent, blood sugar was 95 mg. per cent, serum cholesterol was 332 mg. per cent, blood urea nitrogen 1.7 mg. per cent, and serum electrolytes were within normal limits.

A lumbar puncture was done on January 21. The initial pressure was 290 mm. of water, the spinal fluid had a ground glass appearance and contained 953 white cells (42 per cent of these were neutrophils, 58 per cent lymphocytes). The colloidal gold reaction was 5555210000. The Wassermann reaction was negative. Chemical analysis of the spinal fluid revealed 24.4 mg. per cent of sugar, 750 mg. per cent of sodium chloride, and 113 mg. per cent total protein.

On the day following admission the patient became progressively more stuporous, and a left carotid arteriogram was done. The following day she developed decerebrate rigidity and was totally unable to communicate, but her vital signs remained good. On January 23 a ventriculogram was done. By January 27 she was comatose and had fecal incontinence. At this time Babinski's sign was present bilaterally. She was breathing deeply and regularly. The temperature was septic in type, varying between 99 and 102 degrees.

The patient remained in a comatose state, and on January 29 she suddenly hiccoughed several times and stopped breathing.

Question: On the patient's first admission she had an eosinophilia; were her subsequent eosinophil counts elevated?

Dr. Robert W. Brown (resident in medicine): She consistently had eosinophilia. There were a few of the differential counts which showed only one or two, but the average was around 15 or 16 per cent.

Terry Denison (fourth year medical student):* Were there any neurological signs other than hemiparesis at the time of her last admission?

Dr. Brown: Babinski's sign was present.

Mr. Denison: Was there a loss of pain perception?

Dr. Brown: No, I do not believe so.

Dr. Mahlon Delp (moderator): No specific loss of pain sense was noted. This patient was obtunded a good bit of the time, and one could not really tell whether she was responsive or not.

Question: What was the nature of the sputum? Did it separate out on standing, and did it have a foul odor?

Dr. Brown: I do not believe the odor was described. The sputum was said to be greenish-yellow with a lot of water and mucus in it.

Michael McNalley (fourth year medical student): Were subsequent cultures and skin tests done?

Dr. Brown: She was skin tested on every admission. The histoplasmin was recorded as being equivocal on one admission; otherwise it was considered to be positive.

Question: Was her serum globulin normal?

Dr. Brown: Yes.

Dr. Delp: I think we should mention that there is one positive culture for acid-fast bacilli reported in this chart, and I do not believe it is on the protocol.

Question: Was that positive tubercle bacilli or positive acid-fast organisms?

Dr. Delp: Positive acid-fast.

Dr. Charles E. Brackett (neurosurgeon): Was the spinal fluid cultured?

Dr. Delp: The three cultures of the spinal fluid during her last admission were negative.

Ernie Chaney (fourth year medical student): Is anything known about the nature of the automobile accident? Was she driving, and were there other cars involved?

Dr. Delp: Other cars were involved. It is difficult to get an accurate story about what actually happened. I was interested in whether or not the patient was really injured. She apparently suffered a considerable blow from the accident, but I am not certain whether she was groggy. Some say she was unconscious for a matter of a few minutes, but the patient told me that she was not. I do know that on the following day she was up and around the house and going about her normal activities.

Dr. H. E. Smith (internist): Was she taking cortisone right up to the time of her last admission?

Dr. Delp: Yes.

Dr. Smith: Was a blood sugar done at the same time that the spinal fluid was done on January 21?

Dr. Brown: The blood sugar was done on January 21, 1955, and the spinal fluid was dated January 23, 1955.

Question: The patient apparently had no fractures at the time?

Dr. Brown: No.

Francis O'Kane (fourth year medical student): Did she have chest pain?

Dr. Delp: I am sure that she had at least a dozen episodes of pleural pain.

Question: Did she have expiratory wheezing, and if she did was it throughout the whole chest?

Dr. Brown: Wheezing was described as being present throughout the whole chest. She had some rales throughout both lung bases and some dullness in the right third interspace.

Dr. Delp: She had obvious bronchospasm on numerous occasions when she was examined.

Dr. Brackett: Did she ever have any lymphadenopathy?

Dr. Delp: No.

Mr. O'Kane: Was there pain with her neck stiffness?

Dr. Brown: No, there was not.

Dr. Delp: Will you show the electrocardiograms, Mr. Ney?

Eugene Ney (fourth year medical student): The electrocardiogram taken on May 13, 1949, is within normal limits. The rate is approximately 100, and there is a normal sinus rhythm. The PR interval is 0.12 seconds, the QRS interval is 0.08 seconds, and the QT interval is 0.32 seconds.

The second electrocardiogram was taken on April 26, 1950, at the time of the patient's third admission. The rate at this time is 75 with a normal sinus rhythm. The PR interval is 0.12 seconds, the QT interval is .32 seconds. This tracing is within normal limits.

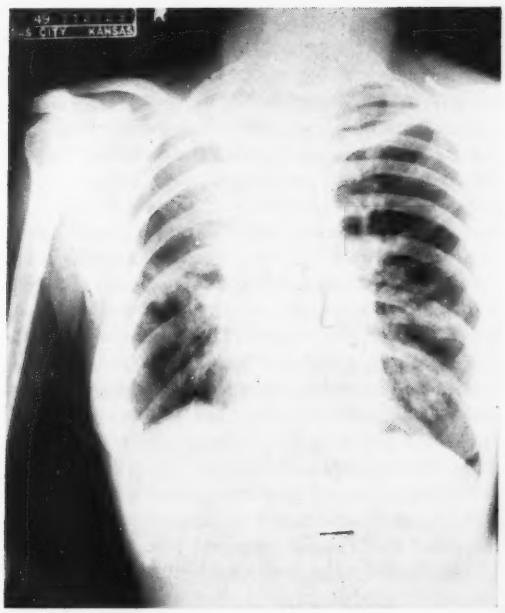
The third electrocardiogram was taken on October 22, 1952, at the time of the patient's fourth admission. The rate is 100. There is a normal sinus rhythm.

Electrocardiograms were taken during the patient's fourth and fifth admissions, and these were also normal tracings.

Dr. Delp: Will you interpret the x-rays, Mr. Penfold?

Richard Penfold (fourth year medical student):

* Though a medical student in February, 1956, when this conference occurred, he, like the others referred to as students, received the M.D. degree in June, 1956.



Figuer 1. Chest x-ray, first admission.

This is the chest x-ray taken on the patient's first admission (Figure 1). The bony structure is normal. I cannot see the trachea very well to tell whether it is deviated, but I believe it is not. The costophrenic angles are clear. The outline of the heart is within normal limits. This is not a direct PA view, so there is a little distortion. There is some soft tissue infiltration in the right upper lung fields. There are increased bronchial markings throughout, and there is some haziness indicating a pleural reaction.

The chest film taken on the second admission, at which time the patient had gained weight and was asymptomatic, shows clearing of the soft infiltrations that were present before. The costophrenic angles are clear. There is peaking of the diaphragms which indicates fibrous pleural adhesions. The contour of the chest throughout is a little bit square, which is consistent with some emphysema (Figure 2).

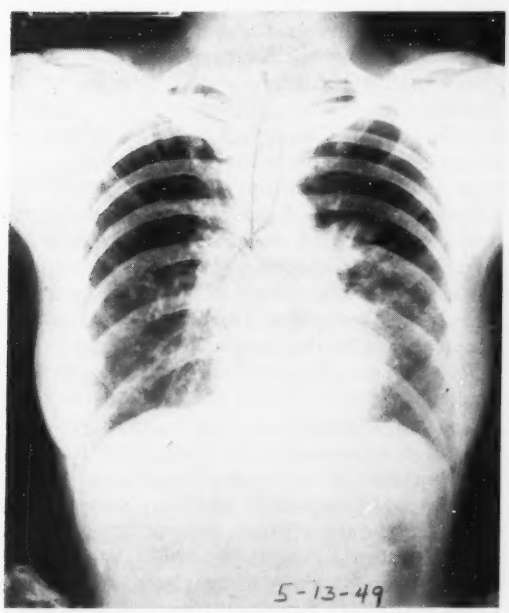


Figure 2. Chest x-ray, second admission.

A bronchogram was taken on the third admission, when the patient had few respiratory symptoms. The soft tissue infiltrations are gone, but I think that there is saccular dilatation of bronchi and bronchioles indicating bronchiectasis (Figure 3).

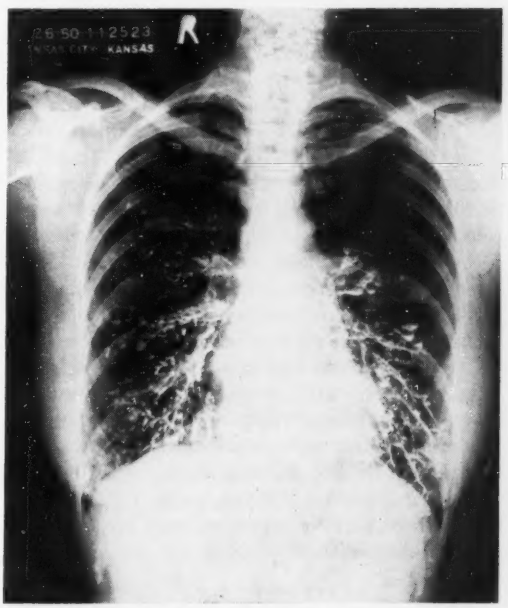


Figure 3. Bronchogram, third admission.

A Waters view of the skull was taken on the patient's third admission. We observe in the left maxillary region some haziness as compared to the orbits. The bony outline is even. This finding is consistent with left maxillary sinusitis.

On the fourth admission the x-ray of the chest shows an increase in the soft tissue infiltration most marked in the right upper lobe. There are large opaque lesions here for the first time, and it is at this time that the patient had a positive culture for histoplasmosis, so I postulate that these lesions could be consistent with aggravation of a primary histoplasmosis. The costophrenic angles are clear. There is some haziness of the pleural surfaces indicating a pleural reaction with effusion.

The chest film made on the patient's fifth admission does not demonstrate the previous lesions, but there is a suspicious lesion which looks like cavitation. The heart shadow is normal.

The final chest film, taken four days before her death, again shows a soft tissue infiltrate in the chest with pleural reaction. The costophrenic angles are clear.

Dr. Delp: Do you have any disagreement with this interpretation, Dr. Tice?

Dr. Galen Tice (radiologist): We did not see a cavity; otherwise his interpretation is all right.

Dr. Delp: This patient also had some arteriograms and ventriculograms. Would you tell us what those showed, Dr. Tice?

Dr. Tice: The arteriograms were reported as normal. I reported the ventriculograms as essentially normal. Filling was poor, which made them difficult to interpret, but they were passed as normal.

Dr. Delp: Dr. Tice, would you care to comment on how many different suggestions you made over a period of eight years about what might be in this chest?

Dr. Tice: Over eight years we made 27 examinations of various parts of the body. The first interpretation was pneumonia, but we could not rule out tuberculosis. As we saw the films at different times the lesion in the upper right chest persisted, and it looked something like a tuberculous scar. Loeffler's syndrome was suggested at one time, because of the high eosinophil count and the shifting pneumonia. Bronchiectasis was verified by the bronchograms. At one time the films suggested a nodular shadow, and the possibility of metastases or even primary tumor was raised. I think that she had pneumonia that kept recurring, and that perhaps she had a tuberculous lesion in the upper right chest.

Dr. Delp: Mr. Neumann, will you give your differential diagnosis?

DIFFERENTIAL DIAGNOSIS

James Neumann (fourth year medical student): Today we are concerned with a 44-year old white woman who came to this hospital about six years before her death with a history of chronic productive cough, weakness, periodic dyspnea, and weight loss. She apparently did reasonably well with medical management until about two and one-half years prior to death, when she was hospitalized with an exacerbation of her presenting symptoms.

Histoplasma were present in the sputum on that admission, and a complement fixation test for histoplasmosis was positive. The patient again did well until four months before her death, when numbness and paresthesis of the left side of her face developed. Two months before her final admission she had suffered a head injury in an automobile accident. During the week prior to this admission she developed a severe headache, vomited, was lethargic, and developed a right hemiparesis. She continued to do poorly and expired on the tenth hospital day.

Initially the differential diagnosis is concerned with chronic productive cough. Heart failure in a 38-year old female without valvular disease, diabetes, or hypertension is unusual, and no clinical signs of failure were present. Bronchogenic carcinoma is not likely to progress so slowly. Pneumoconiosis may be ruled out by the absence of a history of exposure. Patients with pulmonary sarcoidosis exhibit few constitutional symptoms, and fever is unusual. This patient had recurrent febrile episodes. Fifty per cent of sarcoid patients have cutaneous nodules on the face, arms, or back. A slight anemia is usually present. I rule out sarcoidosis primarily on the basis of the severity of this patient's symptoms.

Pulmonary mycotic infections must be considered. Blastomycosis could have produced this patient's symptoms, but it is usually associated with the formation of sinuses from the bones or abdomen. Ninety-two per cent of the patients with disseminated blastomycosis die within two years. I rule out blastomycosis because of the negative skin tests, the absence of characteristic lesions, and the chronicity of the disease.

Coccidioidomycosis produces a primary pulmonary infection which usually heals in a few weeks. If dissemination occurs it usually does so within six weeks after the primary infection, and there usually are subcutaneous lesions. I rule this out on the basis of a negative skin test and the four-year interval since she was in an endemic area.

Actinomycosis occurs most frequently in the male. Lesions extend through the pleura and through the thoracic wall. I rule this out simply on lack of clinical evidence.

Patients with cryptococcosis may have isolated abscesses or subcutaneous masses. The majority of patients with cryptococcosis of the lungs have coexisting cerebral lesions. Therefore, at the time this patient was first seen, I would rule out cryptococcosis on the absence of cerebral symptoms.

I believe that this patient had a subclinical or clinical histoplasmosis at some time before her first admission to account for the positive skin test, but I do not believe that she suffered primarily with histoplasmosis because of the long duration of symptoms. The clinical course in cases of histoplasmosis is usually one and one-half to three months, and during the active phase the complement fixation is usually positive.

I rule out tuberculosis because of repeated failures to demonstrate the organism, the negative skin tests, and the patient's subsequent clinical improvement without anti-tuberculosis therapy. Lung abscess could not be ruled out in this patient until we saw the x-ray,

but I believe that if one had been present for approximately two and one-half years it would not respond to medical management, and she would have been operated upon during the first admission.

I think that she had asthma and bronchiectasis. There is a history of allergy and shots for the relief of dyspnea and coughing; also an elevated eosinophil count strongly suggests asthma. Bronchiectasis may accompany asthma and is particularly likely to occur in those asthmatics who exhibit Loeffler's syndrome. Her early morning sputum is characteristic of bronchiectasis, and we have x-ray evidence of bronchiectasis.

I believe that she developed histoplasmosis prior to her fourth admission, and that she ran a typical clinical course with remissions. I do not believe that dissemination occurred at that time.

I cannot explain the numbness and paresthesis of the left face which occurred four months before her death. She could have had Bell's palsy with complete remission. Her terminal episode was characterized by general and focal cerebral signs. She must have had a lesion in the left frontal lobe involving the motor area. The history of head trauma two months previously would suggest a subdural hematoma, but the cerebrospinal fluid is not compatible with a subdural hematoma.

A brain tumor, particularly a glioblastoma, is compatible with this clinical course, but the cerebrospinal fluid is not typical of a brain tumor. I cannot rule out brain tumor on the basis of cerebrospinal fluid alone.

A brain abscess could produce this clinical picture and is compatible with the cerebrospinal fluid findings. The marked bradycardia which she had is more consistent with a brain abscess than with a brain tumor. In the absence of osteomyelitis of the skull, mastoiditis, or a depressed skull fracture, a hematogenous source is perhaps the most likely one for the formation of an abscess. Bronchiectasis could have provided the focus. A hematogenous abscess more frequently occurs on the left than on the right and is nearly always above the tentorium, usually occurring in the area supplied by the middle cerebral artery. I, therefore, believe that this woman had a brain abscess in the left frontal lobe, and that her death resulted from brain stem compression.

CLINICAL DISCUSSION

Dr. Delp: Mr. Nason, I would like to know what you think this patient's initial illness was. Apparently she had been getting along quite well when she developed an acute illness which had become chronic by the time she arrived here. What do you think was the matter with her? What happened?

Herbert Nason (fourth year medical student): I believe that she had chronic bronchitis which started in 1947. At that time she could have had a primary exposure to histoplasmosis, or developed an acute pneumonia which aggravated the damage which had already been done to the bronchi by an allergic bronchitis or a true bronchial asthma. This precipitated a full-blown bronchiectasis.

Dr. Delp: I think we have inadvertently withheld some information that has to do with some skull films. Someone suggested a petrousitis in this patient. Do you recall these films, Dr. Brackett?

Dr. Brackett: I thought that there was some rarefaction in the petrous pyramids.

Dr. Delp: Mr. Neumann, does this make you want to revise your diagnosis in any manner?

Mr. Neumann: I have revised it too many times.

Dr. Delp: Mr. McNally, what do you think?

Mr. McNally: I believe that she had a brain abscess.

Dr. Delp: Bacterial?

Mr. McNally: I cannot say what caused it.

Dr. Delp: Do you think she had a tuberculous abscess?

Mr. McNally: She could have had a tuberculoma, and she could have had an abscess caused by nocardiosis.

Dr. Delp: Mr. Charles, do you have any ideas about this? What is your diagnosis?

Jess Charles (fourth year medical student): I could not say whether she had a tumor or an abscess, although it is one of the two. I could not find any good explanation for the occurrence of an abscess.

Dr. Delp: Do you think there is any direct relationship between the illness this woman developed in 1947 and her death in January 1955?

Mr. Charles: Bronchiectasis could be the focus for hematogenous dissemination of a brain abscess. I do not believe that histoplasmosis had much to do with her death.

Dr. Delp: Mr. O'Kane, what are your thoughts about the matter?

Mr. O'Kane: I am tempted to stay with tumor.

Dr. Delp: Tell us what kind of tumor.

Mr. O'Kane: It would have to be a rapidly developing one such as a medulloblastoma.

Dr. Delp: Mr. Odim, what do you think was the final diagnosis?

Usim Odim (fourth year medical student): It does not seem to me that there is a disagreement. I think meningitis was present, not that it was the main diagnosis, but I am not able to account for the stiffness of the neck otherwise.

Dr. Delp: Accepting the idea of meningitis now, what about the etiology, etiological agents, pathogenesis?

Mr. Odim: You put me in some difficulty there,

because somewhere in the protocol there was some mention of culturing pneumococci.

Dr. Delp: Mr. Ney, this patient had neurological symptoms and, as a matter of fact, I think she had neurological signs in October prior to her death in January. Do you see any connection between the two?

Mr. Ney: That would seem to indicate that she had a neoplasm rather than a brain abscess. However, I will go along with brain abscess because 5 per cent of those having bronchiectasis develop brain abscesses, and glioblastoma does not occur that often.

Dr. Delp: Mr. Penfold, this patient received antibiotics from 1947 until 1955, and she received cortisone for the last two years of her life. The dosage varied from 50 mg. to 300 mg. in a month, probably not more than that, and she would sometimes go two or three months without taking any cortisone at all. What influence do you think these medications might have had on her terminal illness?

Mr. Penfold: Her terminal illness was, in my opinion, due to a brain abscess. The fact that she was on antibiotics and cortisone would increase the virulence of the organisms and also depress her immunity and inflammatory reaction. If she had a hematogenis abscess from the lung, it could have been a slow smoldering type of abscess seeded a long time before her death.

Dr. Delp: How long?

Mr. Penfold: A brain abscess can go on for years.

Dr. Delp: Eight years?

Mr. Penfold: Yes.

Dr. Delp: Dr. Williamson, may we have your comments?

Dr. William P. Williamson (neurosurgeon): We saw the patient when she was acutely ill with papilledema, right hemiparesis, and a stiff neck. She had chronic pulmonary pathology and, of course, we were concerned whether she had tuberculous meningitis, fungus meningitis, or a brain abscess. We needed spinal fluid badly, but one hesitates to do a spinal puncture if there is increased cerebral pressure, particularly if there is an abscess. So the first definitive test to make it safe to do a spinal puncture was done, namely, an arteriogram to see whether there was a shift of her anterior cerebral arteries indicative of a cerebral mass or whether she had evidence of hydrocephalus caused by a cerebellar mass. A negative arteriogram ruled out an abscess or tumor of any size.

A spinal tap was then done, and it confirmed chronic meningitis of an unknown type on the basis of increased cells, lowered sugar, and increased protein. With no evidence then of intercranial mass, the neurosurgeons tended to relax until the laboratory and medicine departments could determine the etiology of the chronic meningitis. The patient did not relax, however, but became worse, and it was obvious that she was going to die from something before the laboratory could give us a diagnosis. We still could not definitely rule out cerebellar abscess, and for this reason debated whether we should do a ventriculogram. The decision was finally made to do this test, and it was negative, leaving us with a third normal test.

Dr. Delp: Dr. Proud, I brought up the matter of the seemingly damaged petrous pyramid. I think you saw those films, and we discussed this with you. Do you have any thoughts about it at the moment?

Dr. G. O. Proud (otorhinolaryngologist): It has been some time since I have seen the films, but I thought at the time that they were equivocal.

Dr. Delp: Dr. Brackett, do you have any other thoughts about this patient now?

Dr. Brackett: We had evidence of a chronic meningitis and a history of chronic pulmonary infection. In reviewing her x-rays I thought that she did have rarefaction of the left petrous apex and, with negative cultures, I thought that she might have an extradural granuloma involving the fifth nerve in Meckel's cavity and partial compression of the left corticospinal tract.

Dr. Delp: You felt that there was significance to this complaint that the patient had had for four months before her death.

Dr. Brackett: Yes, sir.

Dr. Delp: Dr. Frenkel, will you please present the pathologist's report.

PATHOLOGY REPORT

Dr. Jacob K. Frenkel (pathologist): The culture for Histoplasma was probably erroneously reported to be positive. Dr. Weber took six cultures later, and all were negative. It is worth pointing out that her histoplasmin skin test had been positive ever since 1949, and that in 1949 her complement fixation titer had been 1:50. A culture for tubercle bacilli was reported positive in October 1952, with a moderate growth of acid-fast bacilli. However, three subsequent cultures were negative. The patient's tuberculin reaction was always negative. No Ghon lesion was found at autopsy.

The patient's primary disease was an allergic one. At autopsy we found chronic inflammation of the left maxillary sinus with ulcerations. There was edema, a little hemorrhage, numerous polymorphonuclear neutrophils, but no eosinophils at this time, as the patient had been taking cortisone.

On examination of the lungs we saw extensive bronchitis, some hypertrophy of the peribronchial musculature, patches of inflammation, and some emphysema. Many of the bronchi were outlined by thick, eosinophilic basement membranes, indicative of long-standing inflammation.

In the calvarium we found edema of the seventh

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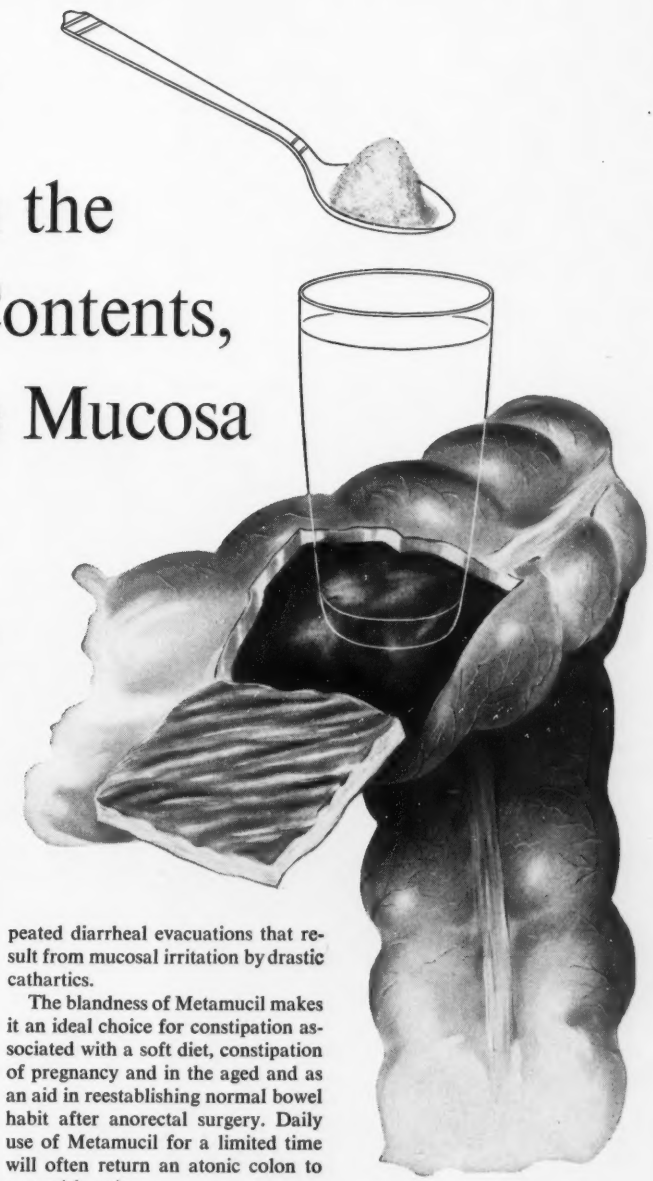

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SEARLE

Figure 4. Gross photograph of granuloma from the petrous ridge.

nerve with loss of myelin and inflammation, but there was no evidence here to show what caused this process.

The patient had ventriculograms, and there was a certain amount of hemorrhage along the needle tracts.

A small tumor (2.5 x 2.0 x 1.5 cm.) was found anterior to the petrous ridge on the left side, as Dr. Brackett had expected. It was glistening and was both intradural and extradural (Figure 4). This tumor was made of chronic inflammatory cells, with giant cells and fibroblastic proliferation, a typical granuloma. Ovoid bodies and septate tubes were found which resembled fungi and stained appropriately with the periodic-acid-Schiff stain (Figure 5). Fungi and granulomatous inflammation were also present in the fifth nerve.

All of the vessels around the base of the brain were involved to marked or moderate degrees (Figure 6). There was arteritis leading to thrombosis and to encephalomalacia of parts of the pons, resulting in death. Much inflammatory reaction was present in the subarachnoid space, together with fungal hyphae (Figure 6). These hyphae were septate, differentiating this fungus from Mucor which can give rise to similar lesions.[1, 2]

Careful examination by Dr. Masahiro Chiga, who performed this autopsy, revealed three small nodules in the lungs. In one of these nodules, which was surrounded by a connective tissue capsule, he found a giant cell which contained fungi morphologically identical to those found in the brain (Figure 7). Both spherules and hyphae were seen.

Our concept of this process is that the fungus was inhaled, that at one time or another it became blood-borne and was carried to the meninges, and that a granuloma developed there. It slowly enlarged and gave rise to basilar meningitis.

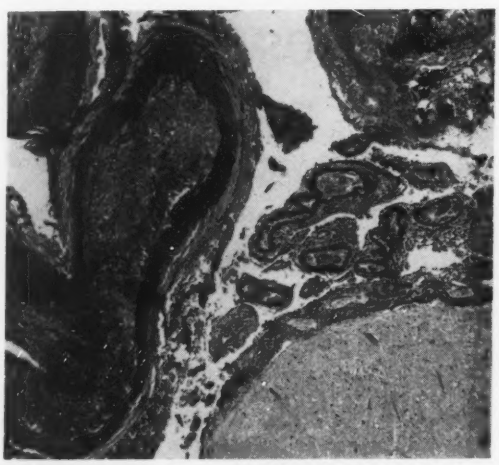

Figure 6. Meningitis and vasculitis with thrombosis of artery at base of pons. PASH. x 40.

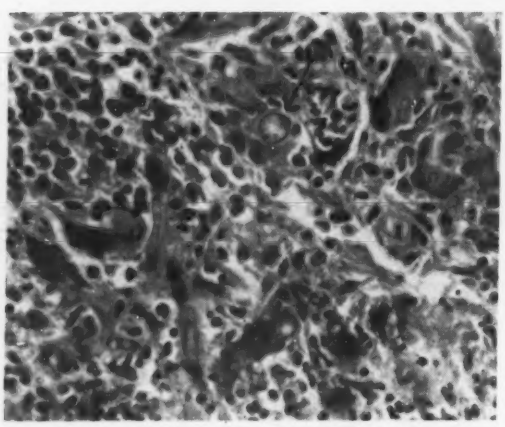

Figure 5. Granuloma from the petrous ridge, showing fungus spherules and hyphae (arrows), accompanied by microabscesses, fibroblastic and giant cell reaction, and by numerous plasma cells and lymphocytes. PASH. x 500.

What are some of the factors that may predispose a patient to develop such lesions? We know that this patient took cortisone for a considerable period of time. I mention this merely as a possibility.

Dr. Alvar Werder has done some work on blastomycosis in mice which is illustrative of the degree of resistance-depression brought about by cortisone.[4] He started out with two groups of 16 mice. After one month without treatment, 13 were still alive. After cortisone treatment for 15 days, only four of the other group of mice were alive, and at 30 days all had died. Cortisone is also known to reduce resistance of the host to other fungus infections.

A further possibility to be considered is the use of antibiotics. It has recently been shown[1] that antibiotics

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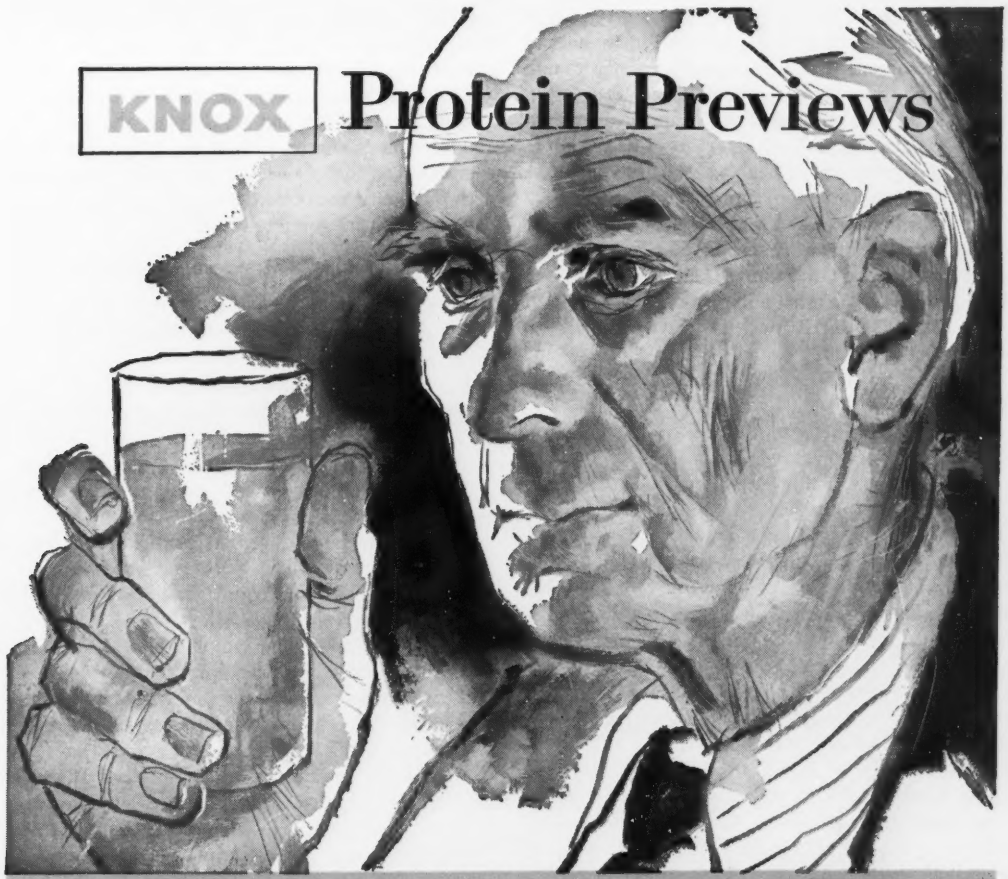

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may predispose the host to fungal infections, not only by the mechanism of reducing bacterial infection and producing a more favorable environment for fungi, but also by their direct growth-stimulating effect. Hence, both host and microbial factors may be involved in making individuals more susceptible to fungal and other infections, particularly when the doses are large and the course of treatment is long.

It should be mentioned that attempts to grow the fungus were temporarily successful, but that no growth occurred on subculture. Hence we were unable to make a more exact etiologic diagnosis.

Dr. Delp: Dr. FitzPatrick, do you have any comments about this case?

Dr. Martin FitzPatrick (internist): Was there bronchiectasis in the left lung?

Dr. Frenkel: There was moderate bronchiectasis but only slight emphysema.

Dr. FitzPatrick: I think it is a fascinating case of a 44-year old woman who had bronchopulmonary allergy, complicated by infection, and ultimate death from the granuloma and meningitis. The vascular lesions which Dr. Frenkel showed are remarkable. We have seen similar lesions in patients with tuberculous meningitis. Recently, with chemotherapy, patients are not dying in the first few weeks; they may live for months and thus have time to develop endarteritic and obliterative lesions and actually get degenerative changes in the brain.

Dr. Delp: Dr. Weber?

Dr. Robert W. Weber (internist): I saw this patient many times before her death. In 1952 she definitely had chronic pulmonary insufficiency and severe bronchial spasm which did not respond to medical therapy. She had severe bronchial spasm and was put on the only drug that would relieve it, cortisone. She took penicillin, broad spectrum antibiotics, and aerosol penicillin intermittently. Most of these could have been factors in her death. The physicians took a calculated risk when these medications were prescribed. When they were started the patient had been an invalid, then for two and a half years she was active and was able to continue her work. This is one of the complications that we see with increasing frequency; with prolonged use of corticoids and antibiotics, these complications are going to occur.

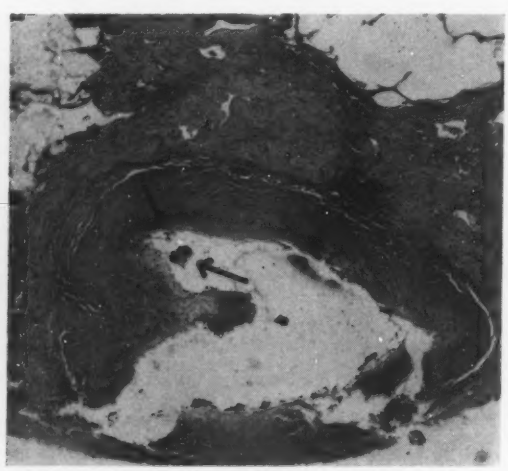

Figure 7. Pulmonary nodule with giant cell (arrow) containing fungus. PASH. x 40.

PATHOLOGICAL ANATOMICAL DIAGNOSIS

Chronic nonspecific sinusitis of ethmoid, sphenoid, and maxillary sinuses (history of sinusitis for a long time before death).

Bronchiectasis involving all lobes of both lungs, moderate (history of asthma and recurrent respiratory infection during eight years before death).

Emphysema of both lungs, slight.

Fibrous adhesions of both lungs to the parietal pleura, moderate.

Hypertrophy and dilatation of the heart, weight 300 grams.

Old fibrocalcified mycotic granulomas in the left lung, with fungi described below.

Partially calcified hilar lymph nodes.

Chronic active mycotic infection involving the meninges, the vessels of the brain stem and base of the brain, the fifth and seventh cranial nerve, with the formation of a circumscribed granuloma (2.5 x 2 x 1.5 cm.) anterior to the left petrous ridge, containing both hyphae and spores of an unidentified fungus (morphologically atypical of the well-known pathogens, culture unsuccessful). (History of numbness of the left side of face three months before death, headache, lethargy, right-sided weakness, coma, and pleocytosis and increased protein content of spinal fluid during two weeks before death.)

Encephalomalacia involving the pons, moderate, secondary to mycotic vasculitis.

Edema of the brain, weight 1500 grams.

Recent surgical incisions in the head, burr holes in the parietal bones, and needle tracts in both frontal lobes (history of ventriculography seven days before death).

Acute passive congestion of the lungs, liver, kidney, spleen, and gastrointestinal tract, slight.

Atelectasis of the lower lobe of the left lung, slight.

Depletion of the lipid of the adrenal cortices, slight (history of cortisone administration for one week before death).

Puncture wounds and ecchymoses in both gluteal regions and antecubital fossae (history of injections and venoclyses during nine days before death).

Vacuolation of the basophilic cells of the pituitary gland, slight.

Cholelithiasis, a pigment stone.

Healed pararectal linear wound in the right lower

little

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quadrant of the abdomen and absence of the appendix (history of appendectomy 16 years before death).

Arteriosclerosis of the aorta, and coronary, cerebral, and pulmonary arteries, slight.

SUMMARY

Dr. Delp: Through the control of bacterial infection and bronchospasm by the use of steroids and antibiotics, a pulmonary invalid of many years was rehabilitated. However, effective as this regimen was in design, the total plan failed in permitting and even fostering the over-growth of a fungus infection, against which there was insufficient defense. Much is yet to be learned of the laws of nature which control infections.

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Clinical Conference in Kansas City

Fifteen nationally known speakers will participate in the 34th annual conference of the Kansas City Southwest Clinical Society, September 24-27. A list of participants will be found in an advertisement on Page 595 of this issue. The program will include lectures, panel discussions, a clinicopathological conference, color television, and daily luncheon quiz periods.

Entertainment on Tuesday evening will be presented in the Pla-Mor and will include a social hour, a buffet supper, a pop concert by 50 members of the Kansas City Philharmonic Orchestra, and two hours of dancing to a 12-piece band.

The complete program for the conference is being published in the September issue of the *Kansas City Medical Journal.*

Medical Assistants to Meet

Medical assistants of the nation will gather in Milwaukee on October 26 for a three-day meeting designed to effect organization of the American Association of Medical Assistants. The first meeting of the group was held last fall in Kansas City, at the invitation of the Kansas Medical Assistants' Society and with representatives of the Kansas Medical Society in attendance.

Most of this year's session will be devoted to business meetings for the entire group, with Sunday set aside for directors' and committee meetings. A Milwaukee brewery will provide entertainment and a buffet supper on Friday evening. A luncheon session on Saturday will include a program with the Rev. Joseph Holleran, director of the Family Living Program of Marquette University, as speaker. At the banquet Saturday evening, following a social hour, Dr. J. E. Manning, Saginaw, Michigan, will speak on "Progress of Research on Medical Assistants' Groups" and "The Medical Assistant of Today."

Two Kansans hold positions of responsibility in the temporary organization, Miss Maxine Williams as chairman and Mrs. Carmen Kline as treasurer. With a secretary and one representative from each of 13 states, they form the present governing body.

A number of Kansas medical assistants will attend the Milwaukee meeting. Registration blanks may be secured from Miss Maxine Williams, 807 Huron Building, Kansas City, Kansas.

A.A.G.P. Building in Kansas City

More than 400 physicians were present at the formal dedication of the new American Academy of General Practice headquarters building in Kansas City on September 1. The four-story building at the corner of Volker and Brookside Boulevards will house the Academy staff and the editorial and business offices of *GP* magazine. The organization, founded in 1947, now has 21,000 members and a staff of 64.

Oklahoma City Clinical Society Conference

The 26th annual conference of the Oklahoma City Clinical Society will be held this year from October 22 through October 25. A large enrollment is expected, and Oklahoma City is becoming increasingly popular as a convention city, now being rated third in the nation.

Sixteen speakers will present the program. In addition to general assemblies, there will be specialty lectures, a new feature this year, and daily luncheon question and answer sessions and a clinical pathologic conference. Entertainment will include dinner meetings, a dinner dance, and specialty group affairs.

All physicians who are members of their county medical societies are invited to attend. The American Academy of General Practice approves the conference for credit under Category 1.

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- In the drug addict

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For intravenous, intramuscular, or oral administration

1. Fazekas, J.F., et al.: J.A.M.A. **161**:46 (May 5) 1956. 2. Mitchell, E.H.: J.A.M.A. **161**:44 (May 5) 1956.

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PHYSICIANS' ACTIVITIES

Dr. Dean Miller, who recently completed a residency at Research Hospital, Kansas City, Missouri, is now practicing in Topeka in association with **Dr. Guy Finney, Dr. Homer L. Hiebert,** and **Dr. Willis L. Beller.** Dr. Miller, who is a diplomate of the American Board of Radiology and Nuclear Medicine, was graduated from the University of Kansas School of Medicine in 1948.

The Nelson Clinic, Manhattan, announces that **Dr. W. Graham Calkins** is now a member of its staff. Dr. Calkins is a graduate of the University of Michigan School of Medicine. After spending two years in the Navy, he went to the University of Kansas Medical Center for a residency in internal medicine.

Dr. Roger F. Eakins, who has been practicing in Goodland, moved to Colorado last month to begin practice in Denver.

A feature story in the *Bonner Springs Chieftain* recently was devoted to **Dr. Karl M. Rottluff,** who was honored by the Rotary Club for 20 years of perfect attendance.

Dr. George E. Burket, Jr., has returned to his practice in Kingman after having spent a year in Boston as a surgical resident at the Massachusetts General Hospital.

Dr. J. Gordon Claypool, who will complete a research fellowship at the University of Kansas Medical Center in December, recently became a diplomate of the American Board of Internal Medicine. He formerly practiced in Howard.

A feature story in the *Wichita Eagle* on July 20 paid tribute to **Dr. Martin Hagan,** who has completed 50 years of practice. Three of his sons are also Wichita physicians, **Dr. Condon T. Hagan, Dr. Daniel J. Hagan,** and **Dr. Francis J. Hagan.**

Dr. A. E. Bair, who has recently been on the staff of the Veterans Administration Hospital in Wichita, has returned to Independence and is resuming his practice there.

The Mission Clinic announces that **Dr. Richard D. Blim** is now a member of its staff. Dr. Blim, a graduate of the University of Kansas School of Medicine, recently completed a residency in pediatrics at the Medical Center.

Dr. Herbert W. Jury, Claflin, who has been in practice 53 years, was the subject of a feature story in the *Claflin Clarion* on July 10.

Dr. Conrad M. Barnes, Seneca, and **Dr. John A. Grove,** Newton, are members of the executive committee of the newly organized Kansas Citizens Safety Council.

DEATH NOTICES

Walter Etna McKinley, M.D.

Dr. W. E. McKinley, 88, an honorary member of the Miami County Medical Society, died at his home in Gardner on July 19. A graduate of the College of Physicians and Surgeons, Keokuk, Iowa, in 1887, he came to Kansas in 1920 and practiced in Grant City and Jewell until 1942, then joined the staff of the Osawatomie State Hospital. He retired to Gardner two years ago. He was a member of the American Psychiatric Association.

John Merritt McGrew, M.D.

Dr. J. M. McGrew, 56, Wellington, died at a Wichita Hospital on July 25. He was an active member of the Tri-County Medical Society and was serving as its president at the time of his death. He was a graduate of the University of Kansas School of Medicine, class of 1927, and specialized in the practice of obstetrics and gynecology.

Donald L. Williams, M.D.

Dr. D. L. Williams, 32, Garden City physician and Finney County health officer, died at a Greensburg hospital on July 25 of injuries suffered in a car accident early that morning. A graduate of the University of Kansas School of Medicine, Dr. Williams had practiced in Garden City since 1953 and was an active member of the Finney County Medical Society.

For an after-school drink that won't "ruin" appetites...

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Chosen as "Man of the Week" in Emporia on July 21 was **Dr. C. H. Munger,** Lyon County health officer for 24 years.

Dr. Floyd E. Muck, who has practiced at the Hertzler Clinic in Halstead since returning from service as a medical missionary in the Belgian Congo, has moved to Caney and is now in practice there.

Dr. James E. Hodgson, Downs, is serving as health officer for Osborne County while **Dr. James E. Henshall,** Osborne, is away for two months touring Europe.

An isotope laboratory was set up at Riley County Hospital, Manhattan, recently by **Dr. Roger Wallace.** The laboratory has been certified for radioiodine uptake diagnostic studies and therapy.

Dr. Thomas P. Butcher, Emporia, announces that **Dr. Richard P. Schellinger** is now associated with him in surgical practice. Dr. Schellinger, a graduate of the University of Nebraska School of Medicine, had a two-year surgical residency in St. Luke's Hospital, Denver, spent a year in Alaska as an Air Force surgeon, completed his surgical residency in Wichita, and then spent two years there as assistant chief of surgery at the Veterans Administration Hospital.

Feature stories about **Dr. Joseph A. Poppen** were published in a number of Kansas newspapers last month on the occasion of his 50th anniversary in the practice of medicine. His home community, Burr Oak, honored him with a celebration on July 31.

Dr. E. Grey Dimond, professor of medicine and chairman of the department at the University of Kansas Medical Center, has been granted sabbatical leave from July 1 to January 1 to travel abroad on a Paul Dudley White Traveling Scholarship. For a 10-week period he will be a Fulbright visiting professor of cardiology at the University of Utrecht, Netherlands.

Dr. William F. Splichal, who has practiced in Belleville since 1931, recently opened an office in Manhattan for general practice.

"Parsonian of the Week" was the title conferred on **Dr. Charles F. Henderson** recently. A story about him was published in the *Parsons Sun,* and his photograph was displayed in an honor spot in the lobby of the Parsonian Hotel.

Dr. A. N. Lemoine, Jr., professor of ophthalmology at the University of Kansas Medical Center, lectured on applied anatomy of the eye and orbit at the Lancaster Course in Ophthalmology at Waterville, Maine, in July.

Dr. William Rottersman, formerly of the Menninger Foundation, Topeka, has entered private practice in Atlanta, Georgia.

A surgical practice has been begun in Kansas City by **Dr. William E. Burger,** a 1951 graduate of Creighton University School of Medicine who recently completed a four-year residency at the University of Kansas Medical Center.

Dr. John W. Turner, Garden City, has been named health officer of Finney County.

Dr. Henry W. Lane, director of the city-county health department in Kansas City, left that position on September 1 to become health officer in charge of the West Seattle-King County, Washington, district.

Having completed a three-year surgical residency at St. Joseph's Hospital, Kansas City, **Dr. William Zimmerman** has now begun private practice in Fort Scott. He is a graduate of Creighton University School of Medicine and a veteran of four and a half years in the Army.

Dr. Tom R. Hamilton, professor and chairman of microbiology at the University of Kansas Medical Center, has been elected to membership in the American Rheumatism Association. He also received a scholarship from Massachusetts Institute of Technology to cover partial cost of a course in Modern Research Methods in Biology and Medicine at Cambridge this summer.

Dr. John R. Shumway, who has been in practice for more than 50 years, mostly in Pleasanton, has announced his retirement. **Dr. Bill Justus,** a graduate of the University of Kansas School of Medicine who interned in Houston, Texas, is taking over Dr. Shumway's practice.

50 *and nine years*

Treating Alcohol and Drug Addiction

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Hypophosphatemic Rickets

Description and Case Reports of Renal Tubular Form of This Deficiency Disease

R. E. PETERSON, M.D., ***Boston***

Infantile rickets is a deficiency disease due to a lack of vitamin D and is characterized by a disturbance of the calcium and phosphorus equilibrium in the blood. Effects of the disease are seen in the skeleton. The incidence has fallen considerably in the past 20 years because of the use of cod liver oil and other sources of vitamin D. It is one of the outstanding accomplishments of preventive pediatrics that florid rickets is now almost a curiosity and mild rickets comparatively rare.[22]

It has long been known that some cases of infantile rickets do not respond to the usual doses of vitamin D, and that rickets can develop in children receiving the usual prophylactic doses of vitamin D. It was not until 1937 that Albright described a severe vitamin-resistant type of rickets. It was pointed out that this disease differs from infantile rickets only by its severity, its failure to respond to the usual treatment, and its response to massive doses of vitamin D.

The disease is characterized by short stature and the usual physical, pathological, and roentgenological findings of florid rickets. Blood studies show decreased inorganic phosphorus, normal or low serum calcium, and a variable alkaline phosphatase. Along with these findings, there is no evidence of kidney, liver, or gastrointestinal disease. Neither is there evidence of any other renal disease.[1]

While the above condition has been established as a clinical entity and is usually called vitamin D resistant rickets, the term may be misleading. The fact that large doses of vitamin D are required to arrest the disease does not necessarily imply that the actual metabolic defect is a resistance to this vitamin. The purpose of this paper will be to discuss the pathologic changes in rickets and the role of calcium, phosphorus, and parathormone in bone metabolism. The clinical picture will be presented along with illustrative cases. The mechanism of the disease will be discussed, and the term hypophosphatemic renal tubular rickets is advanced as more descriptive of the metabolic defect than the term ordinarily used.

This is one of 11 theses, written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school. Dr. Peterson is now serving his internship at Boston City Hospital.

PATHOLOGY OF RICKETS

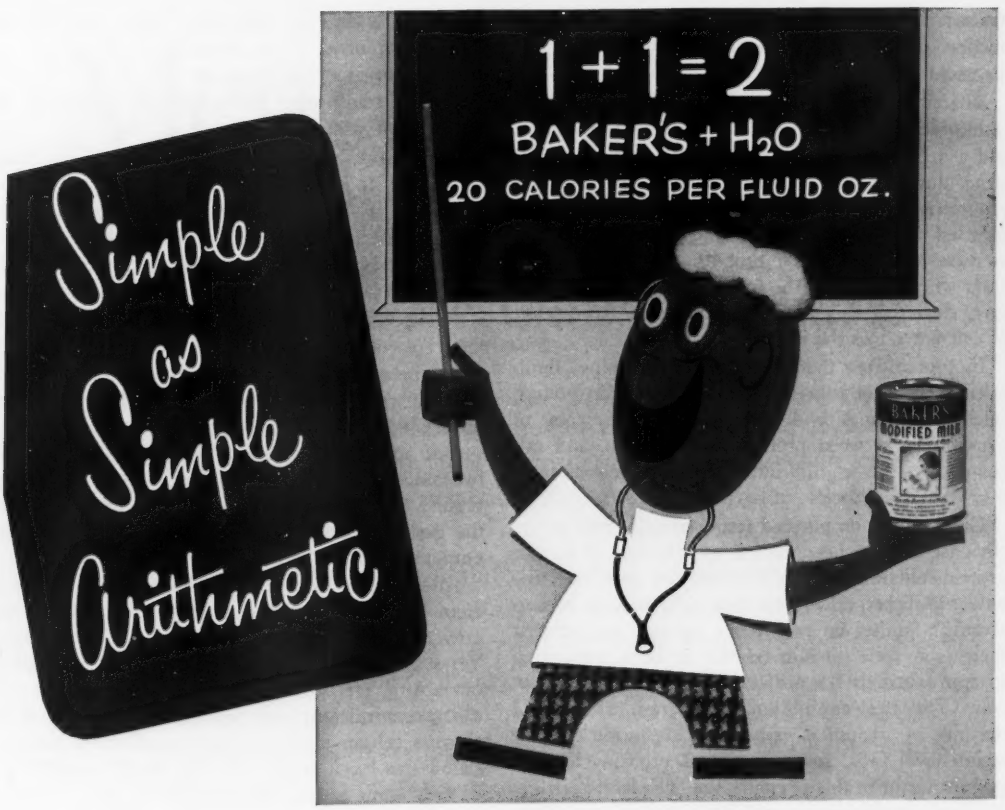
The pathologic changes of rickets are most prominent in those regions where the bone is growing rapidly. The region of the metaphysis is enlarged and easily fractured. The junction between cartilage and bone is irregular, and there are numerous vascularized foci extending into the cartilage from the primitive marrow. The zone of calcified cartilage is entirely absent. In the absence of calcification, osteoid is laid down in increased quantities, resulting in poor quality bone which soon becomes deformed.

Growth in length of the long bones is retarded since this type of growth takes place at the epiphyses. Osteoblasts brought in by capillaries normally build new bone over a calcified matrix. But in this disease capillary penetration is arrested by the excessive amount of osteoid, and the proliferating cartilage cells are not destroyed. This results in the irregular, shortened, expanded "intermediate zone" which is characteristic of rickets. Shortening of the bone and thickening of the epiphyseal area result.[19]

The histologic changes include increased width of the epiphyseal cartilage, failure of epiphyseal cartilage to be reabsorbed, compression of chrondocytes, formation of osteoid tissue, and irregular capillary invasion of cartilage. The defect in rickets is seen to be the lack of provisional calcification and the absence of this necessary zone for bone formation. This is traceable to a deficiency of calcium and phosphate in the area.[21]

CALCIUM METABOLISM

Calcium, one of the two major inorganic constituents of bone, exists in nature in both organic and inorganic form. It is absorbed in the upper small bowel. Absorption is aided by gastric acid which helps maintain the proper hydrogen ion concentration for calcium salt solubility.[4] This calcium-phosphorus ratio of the ingested food is more important than the absolute amount of either element as long as there is not a deficiency. Excess phosphorus will interfere with calcium absorption by forming relatively insoluble calcium phosphate. Conversely, on a low phosphorus diet, excess calcium interferes with ade-



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quate phosphorus utilization. This leads to the production of low-phosphorus rickets, which will be discussed later.[25]

Vitamin D causes increased calcium retention in rachitic infants, resulting in decreased fecal excretion and a negligible increase in urine. In normal adults, large doses of the vitamin initially decrease the proportion of calcium in the urine, but the action is reversed in a few days and the main effect is to increase significantly the proportion of urinary calcium without altering the total excretion. It is, therefore, clear that this vitamin promotes the absorption of calcium across the intestinal wall.[3]

In protein-free fluids such as cerebrospinal fluid, calcium is mostly in the ionized form. In serum, calcium combines with protein and represents an equilibrium between protein, total calcium, and calcium ions; this equilibrium may be expressed by a mass law equation.[11]

Observations on purified serum proteins and on the response of frog heart muscle to solutions of known protein-containing fluids indicate that protein is the only significant calcium-binding substance in human serum.[18] Studies on radioactive calcium suggest that there is a labile calcium fraction in bone amounting to approximately 15 per cent of the total bone calcium. This is at equilibrium with serum calcium and declines as calcium is excreted in the urine and the serum level falls. Ion exchange is probably the important factor in this phenomenon. The labile calcium fraction may represent exchangeable calcium on the surface of the bone crystals.[24]

A survey of available data has appeared to substantiate the view that parathormone exerts its effects on calcium metabolism by a direct action on the bones. Selye has shown that the hormone acts by stimulating the formation and activity of the osteoclasts of bone with the result that calcium and phosphorus are mobilized in increased quantities from the skeletal structure.[6]

It is likewise evident that parathormone does not interfere with calcium reabsorption by the renal tubules. Indeed there is greater reabsorption of calcium in the hyperparathyroid state than under normal conditions. This increased reabsorption of calcium must result from the mass action phenomenon that the renal tubules are presented with greatly increased quantities of calcium in the glomerular filtrate.[13]

PHOSPHORUS METABOLISM

Phosphorus, which is a non-metal, does not occur free in nature but is found in the form of complex mineral compounds and in foods as organic phosphates. The complex organic phosphorus-containing compounds which are ingested must be broken down enzymatically by the pancreatic juices and succus entericus in order to be absorbed in the form of soluble inorganic phosphate in the small intestine. It is then transported across the cell membrane in combination with calcium.

Phosphorus absorption is also dependent upon vitamin D. It is probable that phosphate can be absorbed as an anion with sodium, but ordinarily it is combined in some form of a complex with calcium. Vitamin D promotes the absorption of this complex.[14] Other factors of phosphorus absorption are also related to calcium. A large excess of calcium will interfere with the absorption of both elements. This occurs because the excess calcium will combine with most of the phosphorus and be discharged in the stool while some of the surplus calcium will be absorbed in the form of carbonates, chlorides, and hydroxides. Conversely, if inadequate calcium intake occurs, there is a relative excess of phosphorus in the gastrointestinal tract which will result in excess output of both in the stool.

An adequate level of phosphorus along with calcium and alkaline phosphatase is necessary for the calcification of osteoid and the formation of bone. Yendt and his group studying in vitro calcification of rachitic rat cartilage found that the product of the serum calcium and phosphorus levels must be above a certain figure in order to effect calcification. Below this level, rachitic changes would persist.[27]

Regulation of phosphorus level is then important in bone formation.

Phosphorus is excreted in the urine principally as monosodium and disodium phosphates. It is filtered through the glomeruli in direct proportion to the serum level. It is then reabsorbed in the proximal renal tubules. The role of parathormone in the regulation of serum phosphorus level is controversial and deserves consideration at this point.

Albright has proposed the theory that parathormone, by increasing the urinary loss of phosphate, leads to hypophosphatemia. Following this reduction in phosphate level, the serum becomes unsaturated with respect to calcium phosphate, and calcium then enters the serum from the gastrointestinal tract and the skeleton in increased amounts. Hypercalcemia and hyperphosphaturia result. Ellsworth maintains that the hyperphosphaturia which follows parathormone is caused by a lowering of the renal threshold for phosphorus. These investigators have presented clinical and experimental evidence in favor of this view.[13]

Later, Collip et al., to determine the site of the action of parathormone, carried out experiments on rats. They injected nephrectomized rats with parathormone and later sacrificed them. The lower ends

Meat...

and Its Place in the Diet in Congestive Cardiac Failure

Meat has an appropriate place in the moderate-protein, low-sodium, acid-ash diet advocated in the dietary management of patients with congestive cardiac failure.[1] When extreme sodium restriction is necessary, the meat allowance is regulated accordingly.

Lean meat allows maintenance of a positive nitrogen balance without excessive protein intake, because its amino acids match the quantity and proportions needed for tissue synthesis and repair.[2,3] In the fresh state as purchased it supplies only small amounts of sodium ranging from approximately 50 to 100 mg. per 100 grams. Due to its acid-ash composition (equivalent to 4 to 38 ml. of normal acid per 100 grams of meat) it may facilitate diuresis.[1]

In addition to these important features, meat contributes valuable nutritional factors by virtue of its generous supply of high quality protein, B vitamins, and essential minerals—iron, phosphorus, potassium, and magnesium.

Easy digestibility, a prime requisite of foods eaten by the patient with congestive cardiac failure, is another outstanding quality of meat.

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The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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of the femurs all showed signs of osteoclastic bone reabsorption. From this they concluded that the action of parathormone on the bones is independent of any direct influence it may have on the renal threshold for phosphates.[6]

Fay studied phosphate-creatinine clearance ratios over a wide range of plasma phosphate concentration in normal, parathyroidectomized, and parathormone-treated dogs. He reported no significant differences in the three groups and concluded that there is no apparent alteration in the clearance of phosphate by the kidney after parathyroidectomy or administration of parathormone.[10]

Jahan and Pitts studied renal tubular reabsorption of phosphate under controlled conditions of parathyroid activity and demonstrated that parathormone causes no appreciable depression of serum phosphate level and does not interfere significantly with the capacity of the renal tubules to reabsorb phosphate. Their experimental methods have been questioned, but their conclusions are that the action of parathormone on the metabolism of calcium is independent of any direct influence it may have on the renal threshold for phosphate.[13]

CLINICAL PICTURE

The children who present themselves with refractory rickets will be of short stature because of retarded epiphyseal growth. The epiphyses will be enlarged and prominent, and there will be bowing of the long bones, particularly in the lower extremity. Often a family history of rickets can be elicited. Laboratory findings will consistently be a normal serum calcium and a low serum phosphorus. Roentgenographically, in addition to the deformities noted above, there will be widening of the epiphyseal lines with fuzziness at the metaphyseal end of the epiphyseal plate. The pathologic picture is identical with that previously described for infantile rickets.

Pederson and McCarrol reported on 25 such patients who have been treated in St. Louis. All had a history of rickets beginning in infancy and each had been treated with vitamin D, but in spite of this, florid rickets appeared with the presence of severe deformity in the lower extremities. Sixteen of the 25 patients fell into 10 family groups, and all were of below average stature. In each instance the presence and persistence of deformities had necessitated one or more osteotomies in the lower extremities. The serum calcium was normal or below average in all cases. The serum phosphorus was below normal in all but two cases. The alkaline phosphatase varied from normal to elevated. The Sulkowitch test was negative to a bare trace, as opposed to a one to two plus for normal. Other laboratory tests were normal. There was no evidence of acidosis, disturbed carbohydrate metabolism, or liver disease. The rickets responded only after massive doses of vitamin D, the amount varying with each case. Once healing had begun, the dose could be reduced, but a maintenance dose was necessary.

It was felt that this disease is more common than previously reported and actually represents a common form of dwarfism. The diagnosis can be made by urine analysis and blood chemistry studies including serum calcium and phosphorus.[23]

Myerson presented a case similar to the preceding which showed a low-phosphorus refractory type of rickets which was resistant to vitamin D therapy. He attributed it to faulty renal tubular absorption of phosphate and classified it as a variant to the Fanconi syndrome.[20]

McCune described refractory rickets of the low-phosphorus type in identical twins.[17] Later he described 30 cases in which rickets appeared at the end of the first year of life and persisted despite standard vitamin D therapy. These patients showed a normal serum calcium and a low serum phosphorus. The clinical picture was similar to that previously described.[16]

CASE REPORTS

The following patients, treated at Children's Mercy Hospital in Kansas City, Missouri, are presented as examples of those suffering hypophosphatemic renal tubular rickets:

Case 40917, R. A. R. This 19-month-old Mexican male was admitted to Children's Mercy Hospital on September 10, 1951. He had marked "bow legs" which had been present from birth and which had become more bowed while he was receiving the usual dosage of cod liver oil. His older sister had had bow legs as an infant, but they had since straightened on cod liver oil therapy.

Physical examination revealed a well developed, well nourished Mexican male appearing in good general health, but somewhat thin. The only abnormality noted was a marked bilateral genu varum with lateral ligament instability.

X-ray films revealed increased density in the region of the epiphyseal plate on both distal femurs and the proximal tibiae. There was a slight increase in density about the margins of the secondary centers of ossification in the epiphyses at the proximal tibiae.

Laboratory studies: hemoglobin 8.5 g., red blood count 3,770,000, white blood count 12,300, normal differential, urinalysis normal, non-protein nitrogen 48.5 mg. per cent, thymol turbidity negative, fasting blood sugar 110 mg. per cent, globulin 2.2 g., albumin 5.5 g.

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9-28-51	10.2	2.8	2.2	.....
10- 9-51	9.5	3.6	3.2	normal
10-26-51	9.4	3.4	3.3	sl. increased
11-12-51	12.8	2.5	..	increased
11-27-51	13.9	2.1	..	normal
12-14-51	16.2	1.65	2.35	normal

Hospital course: The patient was placed in a spica cast and treated with 3,000 units of vitamin D daily for 45 days without improvement. He was then given 200,000 units of vitamin D for 15 days, when the dosage was reduced to 100,000 units daily for the same period of time. At the end of the month of therapy, his serum calcium and phosphorus levels were not improved, as often happens, but he was clinically improved. His legs were straighter and the lateral ligaments were tight. His cast was removed and he was discharged on a maintenance dose of 12,000 units of vitamin D daily.

Six months later it was noted that the genu varum was still marked. Corrective wedges were placed in his shoes at this time. One year later it was noted that the legs were straightening nicely. There has been no recurrence of active rickets up to the present.

Case 50502, N. J. S. This three-year-old white female was admitted to Children's Mercy Hospital on November 17, 1954 and again on July 22, 1955. She had had rickets for one year, and the disease was progressively growing worse. She had received cod liver oil until age two. Her mother had had rickets during childhood. Her sister was also in the hospital for rickets (see next case).

Physical examination revealed a white female of average height and weight. Findings were limited to the skeletal system. Wrist epiphyses were enlarged, legs showed genu varum, enlargement below the knees, bowing of the femurs, and coxa vera. An x-ray on November 27, 1954, revealed anterior bowing of femur and tibia and bilateral knock-knees. There was flaring of the epiphyses at the distal radius and ulna. Trabeculations were increased throughout with generalized zone demineralization. The impression was active rickets.

Re-examination on January 2, 1955, showed flaring of the epiphyses with irregularity of the margins, but these rachitic changes were not as pronounced as before. Bone mineralization had improved. The bowing of the femur was unchanged.

The lower extremity deformity, examined on February 24, 1955, was essentially unchanged. The degree of mineralization was approximately the same as the last examination. Further examination on July 2, 1955, presented the same picture.

Laboratory studies: hemoglobin 8.5 g.; red blood count 4,250,000; white blood count 8,080; normal differential, urine negative.

Date	*Calcium*	*Phosphorus*	*Alkaline Phosphatase*
11-18-54	9.1mg.%	4.3mg.%	2.8 K-A units
7-22-55	11.5	2.8	7.1 Bodansky units

Hospital course: During her first admission she was treated with 200,000 units of vitamin D daily for one month with clinical and roentgenological improvement as noted. She was dismissed on 5,000 units of vitamin D per day to be followed as an outpatient. Her second admission was for chicken pox. At this time the calcium and phosphorus determinations were more abnormal than formerly. She was placed in braces and again dismissed on the same maintenance dosage of vitamin D. The disease was arrested during the first hospital stay, but her serum changes persist months later while she is on maintenance therapy.

Case 50593, D. M. S. This seven-year-old white female, the sister of the previous patient, was admitted to Children's Mercy Hospital for varying periods in 1950, 1953, and 1954. She had had rickets since she started to walk, probably since birth. Her legs continued to bow in spite of vitamin D therapy.

Physical examination showed marked genu valgum, rachitic beads at the costochondral junction, and bowing of the tibia and femur.

X-ray films showed changes of rickets consistent with the physical findings. After her course of treatment, films showed the same improvement as was previously described for her sister.

Hospital course: She was treated and improved on 50,000 units of vitamin D for 16 days. A left supracondylar wedge osteotomy was done for previous deformity. She was placed in braces, and her maintenance dose of vitamin D was set at 6,000 units per day. When last seen, in 1955, she was doing well but was still in braces.

Unfortunately, calcium and phosphorus determinations were not done in this case. Other laboratory work was within normal limits. There was no evidence of other disease. The clinical picture was so similar to that of the patient's sister that we include this in spite of the lack of laboratory evidence of a low phosphorus.

DISCUSSION

In presenting these cases, we are not attempting to establish this type of vitamin-resistant rickets as a disease entity, since that has already been done,[1, 16, 17, 23] but rather to illustrate the disease process in detail. These cases fit the criteria for the disease previously described and together point out the facets of the disease usually seen. Instead, we will discuss the experimental production of hypophos-

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phatemic rickets and present evidence that this is a disease of the renal tubule.

EXPERIMENTAL RICKETS

McCollum and Simmonds were able to produce a pathologic condition in the rat similar to human rickets through diet alone. They induced rickets by means of a ration deficient in phosphorus and fat-soluble vitamin A, and in which calcium was present in a ratio considerably higher than the calcium-phosphate ratio which is optional for calcification. They concluded that a specific disproportion of the calcium-phosphate ration, i.e. the calcium high, the phosphate low, was a factor in production of rickets.[15]

Using rats fed purified diets extremely low in phosphorus, but adequate in all other essential nutrients, Coleman produced pathological and histologic changes consistent with the picture seen in human rickets, described earlier in this paper.[5]

Day and McCollum reported on mineral metabolism in animals as follows: The loss of calcium was precipitous during the first two weeks, almost two-fifths of the total loss occurring during that interval. Thereafter the rate of loss diminished. Meanwhile control rats were retaining the administered calcium.

The phosphorus metabolism was also striking. The deficient animals lost phosphorus while the controls retained phosphorus. Only one-eighth of the total phosphorus excreted by the rats on the phosphorus-deficient diet was in the urine, while three-fourths of the excreted calcium followed that route.[8]

Again using rats, Copp and Hamilton demonstrated that low-phosphorus rickets caused radioactive calcium to be lost rapidly from the bones while normal animals fixed the element in the skeleton. While there was rapid uptake by rachitic rats, there was no fixation. This rapid turnover suggests a small and labile calcium fraction in these animals. The plasma calcium clearance in rachitic animals is 10 to 15 times as great as in normal animals and approaches the glomerular filtration rate. So, as calcium is poured out in the urine, the serum calcium level continues to fall as well as the calcium in the labile bone fraction since they are in equilibrium. This is seen where there is a low level of serum phosphorus and appears to be the direct effect of the low phosphorus level on excretion by the kidney.[23]

CONCLUSIONS

The above animal experiments point out that the immediate mechanism of the disease process we are considering is a low plasma level of phosphorus. The radioactive calcium experiments show how this can interfere with fixation of calcium in bone and subsequent ossification, thus producing rickets. Experimental low-phosphorus rickets closely simulates both the pathologic and metabolic changes seen clinically. This, plus the evidence presented to show that parathyroid activity does not directly affect the renal tubule,[6, 9, 12] points to an inherited defect of the renal tubule, namely, its inability to reabsorb phosphate from the glomerular filtrate as the basic metabolic defect in this disease. Dent concurs with this view and states further that the disease is often associated with other congenital tubular defects.[8]

TREATMENT

Treatment of hypophosphatemic renal tubular rickets is based on the threshold concept that a large, individualized dosage of vitamin D will be necessary to arrest the disease process. Vitamin D primarily increases calcium absorption from the gastrointestinal tract and decreases excretion of phosphate by the tubules;[11] but, as shown previously in this paper, this effect must be directly on the renal tubules and not because of secondary decreased parathyroid activity following increased serum calcium.[6, 10, 13] It is known that massive doses of vitamin D will arrest the disease process, but this treatment is not entirely satisfactory. The recommended doses of vitamin D (100,000-500,000 units daily) are the same as those known to produce toxic effects. Vitamin D is thought to raise serum phosphorus level here when it produces slight toxic effects. The bones may be benefited, but one runs the risk of producing renal damage. Metastatic calcifications appear, and the kidneys are likely to calcify with a resultant renal insufficiency.

Since serum calcium and phosphorus both tend to rise, both calcium and phosphate increase in the urine following administration of vitamin D. For this reason urinary calcium excretion (Sulkowitch reaction) must serve as an index of overdosage. Vomiting is also a symptom of overdosage. Clinical improvement and x-ray evidence of healing of bone lesions can be used to set the minimum effective dose. As shown in one of the cases presented, healing will occur in spite of the low calcium-phosphorus product. Long term maintenance dosage can be determined by the same criteria.

Wallace has been studying cases treated with large dosages of vitamin D for some time. He has found evidence of marked renal insufficiency, but the mothers of these children do not necessarily have evidence of renal damage. He doubts that large doses of vitamin D will be advocated much longer.[26]

This leaves one with the administration of extra phosphate salts by mouth in the hope of overcoming renal losses. The oral phosphate does give loose stools, and most people do not regard it as helpful since it does not alter the serum phosphorus level significantly. Darrow gave it with symptomatic relief in one case.[7]

PROGNOSIS

The disease is not curable in the same sense as infantile rickets. It can be arrested, as shown in the

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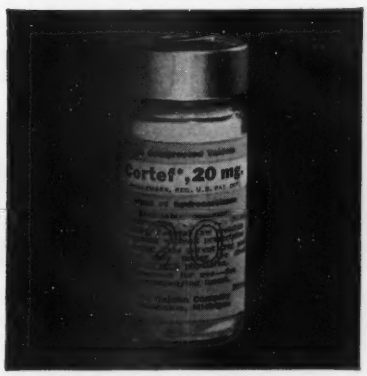

cases presented, but it must be treated continuously and it may recur. After epiphyseal closure and cessation of growth, most patients improve. The resulting condition has been referred to as chemical osteomalacia.[2] Finally, orthopedic procedures including osteotomy to correct deformities and intramedullary nailing to prevent further deformity may be necessary in the long-term management of certain cases.

SUMMARY

Hypophosphatemic rickets, showing the same changes as infantile rickets, is recognized as a clinical entity. The disease has been described and three illustrative cases are reported. Calcium and phosphorus metabolism is discussed.

Experimental and clinical evidence has shown that the basic defect in the production of the disease is the inability of the renal tubules to reabsorb phosphorus. This may be alone, or associated with other renal lesions, and is considered congenital.

Treatment consists of massive doses of vitamin D, although this has not proved to be entirely satisfactory. Oral phosphate administration and orthopedic procedures are advocated as useful.

The name hypophosphatemic renal tubular rickets is advanced as being more descriptive of the disease than the terms previously used.

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Commission on Professional and Hospital Activities

Organization of a Commission on Professional and Hospital Activities was announced in Chicago last month by the American College of Surgeons, American Hospital Association, American College of Physicians, and the Southwestern Michigan Hospital Council.

The commission will conduct a medical statistical service that will help hospitals simplify medical records and analyze records more effectively for improvement of medical and administrative practices. A grant of $260,000 from the W. K. Kellogg Foundation, Battle Creek, Michigan, will support the program for three years, after which it is expected that the service may be continued on a self-sustaining basis.

The commission is an outgrowth of a professional activity study carried on for the last three years by the Southwestern Michigan Hospital Council. The sponsorship of the three national organizations makes possible the broadening of the work and the extension of benefits to many other hospitals.

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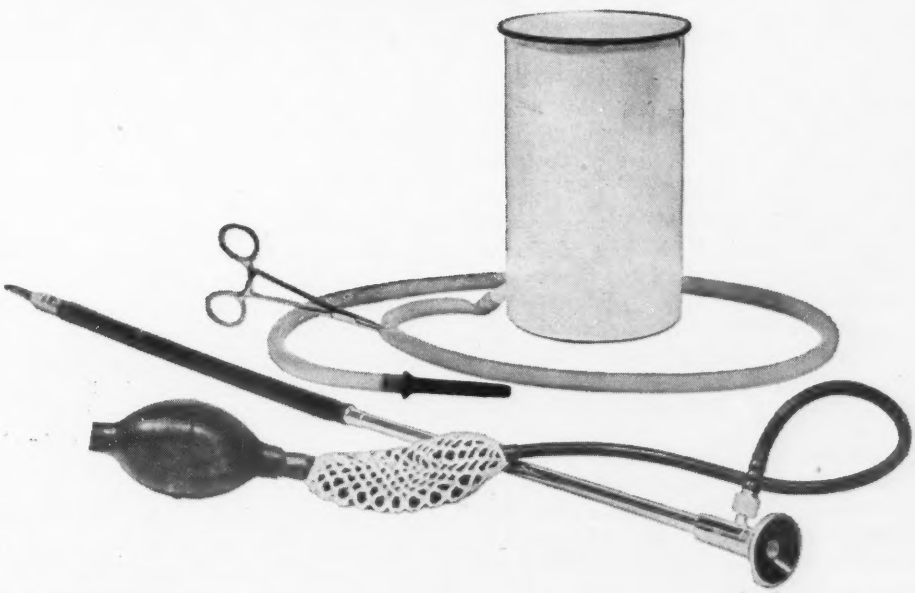

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BOOK REVIEWS

The Morphology of Human Blood Cells. By L. W. Diggs, M.D., Dorothy Sturm, and Ann Bell. Published by W. B. Saunders Company, Philadelphia. 181 pages, 31 color plates, 54 figures. Price $12.

This book is not one that would be of special value to the general practitioner unless he were especially interested in hematology. There are several hundred good illustrations of various kinds of cells, blood, metastatic malignant cells, and tissue cells, showing their structure and characteristic features. The pictures dealing with sickle cells are unusually good. Little technique is given, but there are a few simple procedures on making slides, stains, etc. It is an excellent book for the worker in hematology, either technician or pathologist. There are also good pictures of lupus erythematosus cells and fixed tissue cells of bone marrow.—*J. L. L.*

Treatment of Heart Disease—A Clinical Physiologic Approach. By Harry Gross, M.D., and Abraham Jezer, M.D. Published by W. B. Saunders Company, Philadelphia. 549 pages, 91 figures. Price $13.

Contents of this book are logically grouped in seven sections: The Basic Mechanisms of Cardiac Symptoms and Their Managements; Hypertensive and Arteriosclerotic Heart Disease; Diseases of the Heart Secondary to Inflammation; Congenital Heart Disease; Surgery in the Cardiac Patient; Disorders of the Heart Secondary to Metabolic Disorders, and Emotions, Adjustments and Rehabilitation in Heart Disease.

Only one of the extremely satisfactory features of this volume is the consistent construction of sound methods of treatment and management upon clear expositions of the disturbed physiology. Such a virtue is bound to appeal to both the critical student and the sophisticated clinician.

Coverage is broad, adequate, and properly apportioned according to the relative importance and frequency of the various cardiac problems.

Picking at random an example of thoroughness of discussion, we find the treatment of arteriosclerotic heart disease beginning with a discussion of the disturbed physiology, a brief discussion of clinical variations, medical treatment with all of the modern drugs and procedures, as well as a complete discussion of the surgical treatment.

Surgery in the cardiac patient is usually presented as an afterthought in textbooks of cardiology. Here it is properly and exhaustively treated.

Compactly bound, well printed, and quite readable, this is a book deserving many printings.—*M. H. D.*

Pulmonary Carcinoma—Pathogenesis, Diagnosis and Treatment. Edited by Edgar Mayer, M.D., and Herbert C. Maier, M.D. Published by J. B. Lippincott Company, Philadelphia. 540 pages. Price $15.

This well-written and compiled book effectively covers the field of pulmonary carcinoma. The authors have pointed out that this would be an excellent book in the hands of the general practitioner. However, it is an excellent book in the hands of anyone interested in the prevalent disease of carcinoma of the lungs.

In the foreword to the main volume itself, by Charlotte S. Cameron, it is pointed out that extirpolation of the present rate of rise indicates that lung cancer will soon be the concern of every family doctor. Mention is made of the role of the doctor in relationship to the patient with hopeless carcinoma.

The book effectively points out the effective and actual increase in the incidence of pulmonary carcinoma in the past few decades. An attempt was adequately made to encompass all the facets of pathogenesis, diagnosis, and therapy.

A discussion of possible etiologic factors is presented, together with various experimental approaches to lung cancer. The pathology of pulmonary neoplasms was presented from the standpoint of clinical correlation. The very last of the volume presents case reports illustrating common problems in diagnosis and management. An attempt is made to analyze the various diagnostic procedures, with reference to their value to the clinician and to the diagnostician. Chapters on radiation therapy, chemotherapy, and the use of isotopes, together with the medical management of inoperable cases, gives the clinician a complete survey of all aspects of this unfortunate disease.

Surgical therapy is discussed and analyzed. An assessment of indications for surgery and results therefrom is made.

All of the phases of diagnosis are covered, each in a separate chapter and by a separate and distinguished author. These include pathology, biology, and environmental aspects of lung cancer. The diagnosis of this disease is thoroughly covered in chapters on the clinical aspects of bronchography, exfoliative cytology, and radiology.

In addition to material on surgical therapy, radiation therapy, and the use of radioisotopes, there are additional chapters on chemotherapy and medical management.

At the end of the volume, preceding the case histories, is a provocative and well written thesis on "The Outlook for Cancer" by Cornelius P. Rhodes.

This is an excellent book of value to anyone interested in this unfortunate malady.—*J. G. S.*

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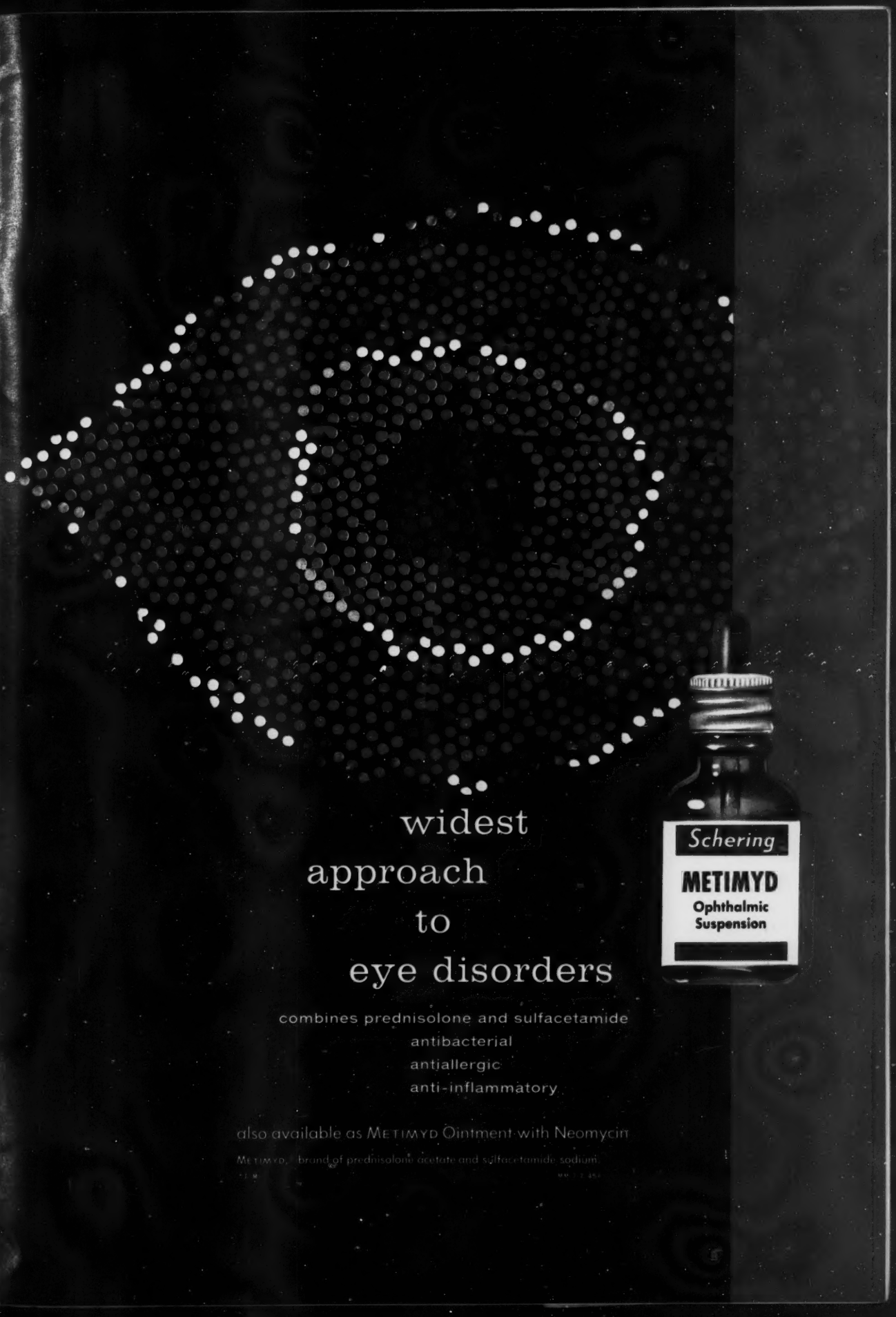

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By arrangement	EXFOLIATIVE CYTOLOGY

Garb, M.D. Published by Springer Publishing Company, Inc., New York. 160 pages. Price $2.00.

This book is good in many ways. First, it describes the proper collection of specimens and stresses good specimens as prerequisites of dependable laboratory results. If the patient is to have a special diet, fasting, or bed rest preceding a test, then a note of instruction is given. Many helpful normal values are given, and under each test is a statement as to its significance, body function, or pathological importance. If a test is contraindicated, the author states the fact, as Bromsulphalein retention when jaundice is present.

Second, this material is well arranged. For tests performed on various body fluids, the name of each test is given and information on how each fluid is treated; for example, the test for methemoglobin is performed on whole blood, which means an anticoagulant would be added. Tests are also grouped as to organ or function of that part.

The author has successfully written a book for student and graduate nurses. In a small laboratory, the book would be useful as a quick reference. For the student technologist, little technique is given; for the medical technologist, many explanations of principles are over-simplified.—*W. N. and L. H.*

Bellevue Is My Home. By Salvatore R. Cutolo, M.D. Published by Doubleday and Co., Inc., New York. 317 pages. Price $4.00.

Bellevue Hospital, a medical city of roughly 9,700 population, would be impressive to some because of its size. Others might find it interesting because it operates on an annual budget of $17,000,000. Still others might think of its personnel—1,000 visiting doctors, 459 interns and residents, 583 graduate nurses, 302 practical nurses, 500 student nurses, 1,322 attendants, 1,000 volunteers, 1,890 salaried personnel —and a daily average of 2,700 patients.

But to Dr. Cutolo, medical superintendent of the hospital, Bellevue is home. He has been there for 25 years. The warmth of the word "home" sets the tone for the book. Instead of seeing patients as statistics, he sees them as individuals; instead of seeing physical properties, he sees means for rendering help to those who need it. It is obvious that he finds satisfaction in his profession, stimulation in his work, and reward in service.—*P. F.*

Experimental Tuberculosis Bacillus and Host. Ciba Foundation Symposium. Published by Little, Brown and Company, Boston, for Ciba Pharmaceutical Products, Inc., Summit, New Jersey. 396 pages. Price $9.00.

A symposium on "The Tubercle Bacillus and the Reactions of the Host Tissues" was held in England in October, 1954, at the invitation of the Ciba Foundation, London. Leading research workers from different countries attended.

Tuberculosis is still a major disease and kills more persons than any other single cause of disease between 15 and 35 years. In most countries the number of new active cases continue at a high level, even with improved methods of treatment. The continued study of the fundamental nature of the bacillus, the basic pathogenesis, and of host reactions is necessary.

The symposium consisted of 24 scientific papers, including the opening and closing remarks, with discussions on tuberculosis, plus four papers on leprosy. These papers were given by internationally recognized scientists. Some of the subjects discussed were: the proteins, polysaccharides, and mycolic acids of the tubercle bacilli; early tissue reactions to the tubercle bacilli; biochemical factors which may influence the fate of the tubercle bacilli in tissues; bacterial components concerned in the early phase of infection; the serology of tubercle polysaccharides and various fractions of culture filtrates; chemical nature of the lipoidal factor of the tubercle bacilli responsible for the induction of tuberculosis hypersensitivity; tuberculosis hypersensitivity and desensitization; the mechanism involved in acquired immunity; the role of bacterial multiplication in establishment of immunity; and human lung tissue reactions to the tubercle bacilli in relation to chemotherapy.

The papers were good and discussions which followed most interesting. For all persons interested in tuberculosis, whether basic research or in clinical work, this book is recommended.—*C. A. H.*

Handbook of Toxicology, Volume I. Edited by William S. Spector. Published by W. B. Saunders Company, Philadelphia. 408 pages. Price $7.00.

This 408-page paper-bound volume was prepared under the direction of the committee on the handbook of biologic data, division of biology and agriculture, the National Academy of Sciences, the National Research Council. It presents tabular data on the acute toxicity of many substances for several species of commonly used laboratory animals. These toxicities were determined by oral or parenteral administration or inhalation.

The principal contributor was Wolfgang F. von Oettingen, M.D., Ph.D., chief toxicologist of the National Institute of Health, Bethesda, Maryland. The guiding principle in the selection of material was that it be of basic importance and that the literary sources be reliable. Some valuable data was omitted, either because they were not on hand for publication or because there was insufficient time for preparation for printing. They did not exclude

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data because it had been previously compiled or was available in other forms.

The objective of clarity of presentation was met successfully. They did this by selecting fundamental data for the body of their tables and by the concurrent use of abundant numbers of footnotes. Emphasis was placed on the fact that values given in their tables are by no means absolute, and subsequent interpretation should use listed values only as a yardstick of toxicity for the compounds listed. The authors recognize that the data, particularly in the field of acute toxicity, are subject to perpetual revision as investigators improve and standardize their techniques and gather more data.

The entire book is composed of two tables. The first table is entitled "Lethal Doses of Solid and Liquid Compounds; Laboratory Animals." The second table is entitled "Lethal Concentrations of Gases, Vapors and Fumes in Respired Air: Laboratory Animals." The first table is 319 pages; the second table is 42 pages. The index occupies the remainder of the book.

The subsequent volumes are scheduled to include the following:

Volume II—Physical, chemical, biological, and toxicological properties of antibiotic, antihelminthic, antiamebic, and antimalarial compound; a survey of chemical carcinogenic agents; metabolites of toxic compounds.

Volume III—Physical, chemical, biological, and toxicological properties of insecticides, fungicides, rodenticides, and herbicides; residues of pesticides on (or in) foods; minimum lethal concentrations of pesticides to domestic animals, farm animals, and wild life.

Volume IV—Toxic and venomous animals; toxic plants; alkaloid; poisons and poisonings (compounds, symptoms, antidote and treatment); histologic and physiologic effects of poisons; toxicities of ingredients of commonly used commercial products; toxicities of natural substances occurring in foods.

Volume V—Toxicities of potential water pollutants; maximum allowable concentrations of toxic substances in air, drinking water, and food; agents and symptoms of chronic toxicities; skin toxicities; industrial toxicology; radiation toxicology.

Some 28 additional contributors were active in preparation of Volume I. From the above it is surmised that the five volume reference will constitute a most important encyclopedic reference for the toxicologist, the pathologist, the pharmacologist, and medical consultant. It is dubious that the encyclopedia will have much to offer the generalist.—*N. V. T.*

Physical Diagnosis. By Ralph H. Major, M.D., and Mahlon H. Delp, M.D. Published by W. B. Saunders Company, Philadelphia. 358 pages, 536 figures. Price $7.00.

This is an excellent revision of an already well written and established textbook in physical diagnosis. The original author is well known to most students of medicine and history of medicine and welcomes the co-authorship of Dr. Mahlon Delp who, for the past two decades, has been an outstanding teacher of physical diagnosis and professor of medicine at the University of Kansas School of Medicine.

The new edition contains many revisions; some paragraphs and chapters have been rearranged; excellent new illustrations have been added, and newer clinical entities are described.

The text adheres strictly to physical diagnosis and refers only to the other diagnostic aspects of disease when it clarifies the explanation.

This book should constitute a part of the medical library of every student of medicine and should be read and reread by all physicians interested in improving themselves in the practice of medicine.—*C. C. G.*

A Dictionary of Dietetics. By Rhoda Ellis. Published by Philosophical Library, Inc., New York City. 152 pages. Price $6.00.

This book contains definitions of terms and references related to diet and diet therapy. The definitions are in a simple and understandable form. The book would be of value to a lay person in charge of the dietary department of a small hospital.—*V. G. H.*

Management of Menstrual Disorders. By C. Frederic Fluhmann, M.D. Published by W. B. Saunders Company, Philadelphia. 350 pages, 121 figures. Price $8.50.

While the author has presented little new material, he gives a well organized review of the subject aimed primarily at the medical practitioner. The various menstrual disorders, diagnosis, and treatment are discussed separately, but their place in the general health of the individual has been kept. He emphasizes the danger of mistaking pathological uterine bleeding for abnormal menstrual bleeding.

The chapters on Gonadotropins, Steroid Hormones, and Control of Menstruation are basic and make a firm footing for the clinical discussions which follow.

The final chapter, devoted to clinical usage and commercial preparations of sex hormones, should have a practical value for every practitioner.—*N. H. O.*

Diseases of the Skin. By Richard L. Sutton, M.D.

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Published by C. V. Mosby Company, St. Louis. 1479 pages. Price $29.50.

The publication of this book is a major event in medical literature. It is the 11th of a series begun in 1916; the third to bear the name of R. L. Sutton, Jr.; the first to bear only his name.

The book embodies several changes from previous editions. The most important is, perhaps, the organization. Dr. Sutton has organized the bulk of his book on the basis of etiology rather than morphology. But the usual chapters on basic sciences, such as anatomy, embryology, etc., are included. The size is bigger than ever, and to avoid publication in two volumes, the type size has been reduced.

The method of reference presentation is another change. The whole reference is sandwiched into the text. Line readers will find this jars them and slows them at first. Postscripted to each section there is additional bibliography with a word or sentence describing the article. This is an extremely valuable innovation and allows the reader to identify at once the particular facet of the literature he might wish to pursue.

Dr. Sutton has mentioned *everything* and discussed most things thoroughly. The discussion is never ponderous, and for the most part is immensely readable. Although the book is largely a catalogue of symptom pictures—and a most comprehensive one—it escapes being dull by the constant introduction of the author's opinion of all these ideas that have been stated by others. In the realm of therapy, the accepted modalities are all given and discussed, and the author is not reticent in stating his own views.

The book's major weakness and its strength are one and the same, vis., its immensity. This is no book to read in bed or to hold in one's lap—it weighs too much; but if one wants a thorough, well written discussion of anything dermatologic it will be herein contained.—*C. M. L., Jr.*

ANNOUNCEMENTS

Postgraduate courses in all specialties, University of Nebraska College of Medicine. Schedules and information available from Postgraduate Affairs, University of Nebraska College of Medicine, 42nd and Dewey Avenue, Omaha 5, Nebraska.

Second annual meeting, American Rhinologic Society, Chicago, October 9-13. No registration fee. Physicians invited. Write secretary, 834 Wellington Avenue, Chicago 14, Illinois.

Convention, American College of Gastroenterology, Roosevelt Hotel, New York City, October 15-17. Annual course in Postgraduate Gastroenterology, Roosevelt Hotel and Metropolitan Hospital Center, October 18-20. Advance registration required. Information available from College, 33 West 60th Street, New York 23, New York.

Seventh annual conference, National Association for Music Therapy, Hotel Jayhawk, Topeka, October 18-20. Registration fee $5.00. Margaret Sears, Publicity Chairman, Topeka State Hospital, Topeka.

Meeting, Midwest Group of Medical Library Association, Henry Ford Hospital, Detroit, October 12-20.

School Health Conference, University of Kansas Medical Center, October 22 and 23. First day, discussions on heart disease; second day, pulmonary disease. Write Postgraduate Medicine, 39th and Rainbow, Kansas City 12, Kansas.

Postgraduate course in obstetrics, University of Kansas Medical Center, November 1-3. Registration fee $35. Write Department of Postgraduate Medicine.

Meeting, American College of Obstetricians and Gynecologists, Palmer House, Chicago, November 7-9. Information and programs available, 116 South Michigan Avenue, Chicago 3, Illinois.

Clinical Symposium, Management of Carcinoma of the Breast, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, November 9 and 10. Physicians invited.

Course in internal medicine, University of Kan-

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In preparation for the observance of The Kansas Medical Society's centennial anniversary, members of the Committee on History are attempting to collect all material of historical interest. Physicians who can contribute information, records, etc., are urged to send such to

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sas Medical Center, November 12-15. Registration fee $50. Write Department of Postgraduate Medicine.

Course 5, American College of Physicians, University of Oklahoma School of Medicine, Oklahoma City, November 26-30. Fee to members $30; others, $60. Write the College, 4200 Pine Street, Philadelphia 4, Pennsylvania.

Meeting, Association of Military Surgeons of U. S., Statler Hotel, Washington, D. C., November 12-14. Suite 718 New Medical Building, 1726 Eye Street, N.W., Washington 6, D. C.

Meeting of American Public Health Association and 40 related organizations, Atlantic City Convention Hall, November 12-16. Write 1790 Broadway, New York City.

Postdoctoral fellowships available, preparation for careers in research or academic medicine or in clinical fields of psychiatry, rehabilitation, orthopedics, management of poliomyelitis, and preventive medicine. Awards for one, two, or three years. Write National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

Prize of $350 offered for best essay on "Present Day Treatment of Infertility," Rhode Island Medical Society. Deadline January 10, 1957. Write Caleb Fiske Fund, 106 Francis Street, Providence 3, Rhode Island.

American Goiter Association offers Van Meter prize award of $300 for best essay on original work on problems related to the thyroid gland. Deadline January 15, 1957. Write Association, 149½ Washington Avenue, Albany 10, New York.

Essay contest, contributions on diagnosis and treatment of chest disease (heart or lungs), sponsored by American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois. Prizes of $500, $300, $200. Deadline for entries April 10, 1957.

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*Modell, W.: The Relief of Symptoms, Philadelphia, W. B. Saunders Company, 1955, pp. 265-266.

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Appointments to Staff at K.U.

Appointments to the staff at the University of Kansas School of Medicine were announced recently by Dean W. Clarke Wescoe. Some are on a part-time basis. They include the following: pathology and oncology, Dr. James B. Caulfield, instructor; Dr. Bernard Klionsky, instructor; Dr. Martin Lambert, instructor; pediatrics, Dr. George R. Dubes, assistant professor; Dr. Italo Archetti, associate professor; Dr. R. D. Blim, instructor; Dr. Mary S. Boyden of Lawrence, instructor; medicine, Dr. W. Graham Calkins of Manhattan, instructor; Dr. James C. Dowell of Lawrence, instructor; Dr. Clarence M. Pickard, instructor; Dr. Sherman M. Steinzeig, instructor; Dr. Carl J. W. Wilen of Manhattan, associate; surgery, Dr. John M. Hansen, assistant professor; Dr. C. S. Stotts, assistant; Dr. Robert W. Wright, assistant.

Physical Examination of Doctors

The need for physical examination of doctors was pointed up by a study of tests given physicians who visited a certain booth at the American Medical Association meeting in Chicago in June. The booth, carrying a sign, "A Yearly Physical Examination for Every M D.," was sponsored by the A.M.A. Section on General Practice, the American Academy of General Practice, and the National Tuberculosis Association.

Chest x-rays were given 965 physicians with negative findings in 83.5 per cent. But tuberculosis was suspected in 58 (6 per cent), there were cardiac findings in 42 (4.3 per cent), and other pathology was found in 59 (6.1 per cent).

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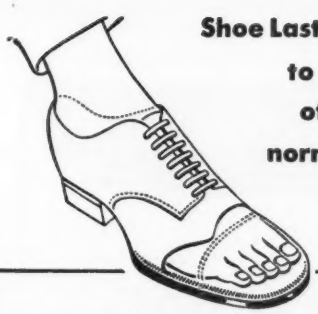

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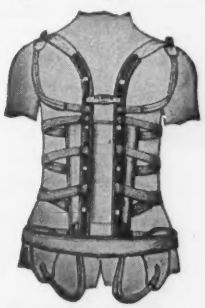

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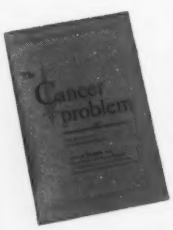

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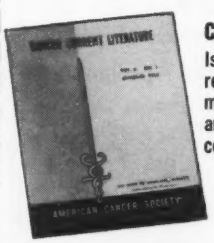

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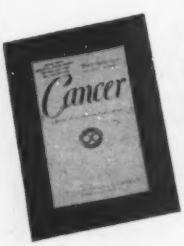

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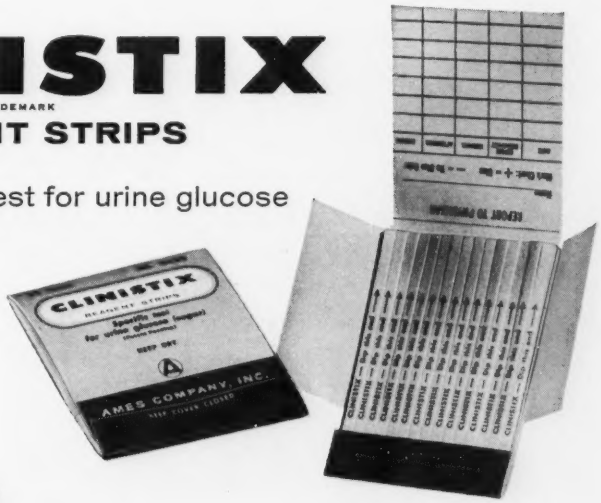

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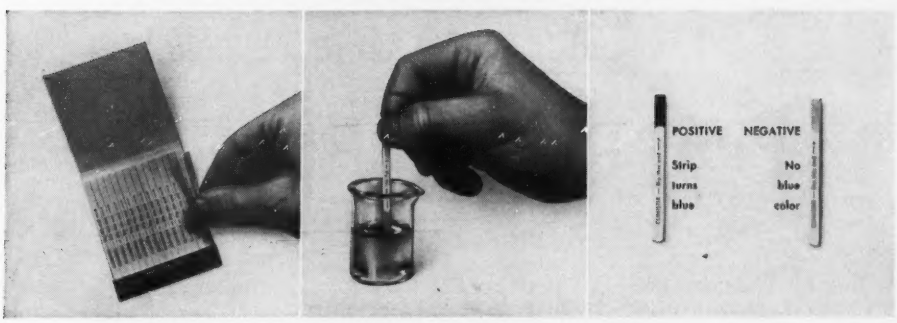

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